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VOLUME FOUR

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IMPORTANT ANNOUNCEMENT

The increase in the output of papers in the field of mathematical biophysics makes it difficult to insure prompt publication without an increase in the size of the journal. Therefore, the Bulletin of Mathematical Biophysics inaugurates the following service:

Upon acceptance of a paper, the Editor, if necessary, will ask the author to shorten the paper to an extent dictated by the requirements of a reasonably prompt publication. The shortening should in no case reduce the paper to a mere abstract. Such a shortened paper will be published within six months or less.

The unabbreviated original manuscript will be kept on file at the editorial office. Any person desiring to avail himself of the complete manuscript, may obtain promptly a microfilm copy of the latter, at the cost of 1¢ per page plus postage, by applying to the Editorial Office, 5822 Drexel Avenue, Chicago, Illinois.

All papers in the Bulletin which have been thus shortened, will be marked at the end by the symbol MF, followed by a figure, indicating the number of doublespaced typewritten pages of the unabbreviated manuscript.

A MATHEMATICAL THEORY OF PROTOPLASMIC PROTRUSIONS. I

HENRY E. STANTON
THE UNIVERSITY OF CHICAGO

The theory of cellular elongations is applied to a particular case of a spherical cell with a cylindrical protrusion under the conditions of equilibrium, and conditions for continued and arrested growth are examined.

N. Rashevsky (1940) has developed and proposed a theory of cellular elongation derived from the mechanism of diffusion forces with primary reference to the phenomenon of cell division. We shall apply the same general theory in this paper to a particular type of cell configuration, wherein the main body of the cell will be considered spherical and a cylindrical protrusion has been extended from this main body. In any metabolizing cell, the diffusing substance or substances will exert a drag on the cell structure, assuming that the diffusion takes place through some type of gel, and these diffusion forces together with osmotic pressure at the membrane and surface tension will cause deformation of the cellular shape under certain conditions.

With these ideas, N. Rashevsky, and others have shown that the relative elongation in the z -direction is given by the formula,

$$\frac{1}{L_z} \frac{dL_z}{dt} = \frac{1}{3\eta V} \left\{ -\frac{3RT\mu}{2M} \int_s c \{ z \cos(\nu, z) - \frac{1}{2}[x \cos(\nu, x) + y \cos(\nu, y)] \} dS + \int_s [zZ_\nu - \frac{1}{2}(xX_\nu + yY_\nu)] dS \right\} \quad (1)$$

where

(x, y, z) = coordinates of the surface elements dS ,

c = concentration at that point,

X_ν, Y_ν, Z_ν = components along the coordinate axes of the forces normal to the element dS ,

ν = a unit normal to the surface element,

V = the total volume of the cell,

μ = the fraction of this total volume which is filled with semi-rigid structure,

η = the coefficient of viscosity of this structure,

R = the universal gas constant,

T = the absolute temperature,

L_z = the length of the cell along the z -axis, along which the elongation is assumed proceeding.

The components of the surface forces X_ν , Y_ν , Z_ν arise from the pressures, one of which is the osmotic pressure resulting from the change in concentration across the membrane,

$$p = \frac{RT}{M} (c - c') \quad (2)$$

where c' is the concentration adjacent but outside, and the pressure arising from the surface tension,

$$p' = -\gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \quad (3)$$

where R_1 and R_2 are the principle radii of curvature at the point on the surface. These quantities are equivalent to hydrostatic pressures and are, therefore, directed along the normal to dS .

The geometrical arrangement of the cell is shown in the diagram, and from this it is clear that the computations can be separated into three convenient parts, the main spherical body, the cylindrical sides of the protrusion and the end of the protrusion. We will consider first the evaluation of the integrals on the right side of (1) over the main spherical portion of the cell.

It will be assumed that c_2 is a constant over the surface of the region, and that θ' represents the angle subtended at the center of the sphere by the intersection curve of the protrusion, also considered a constant in these calculations. Then, for any point on the surface it is clear that

$$\cos(\nu, x) = \frac{x}{r'_2}, \quad \cos(\nu, y) = \frac{y}{r'_2}, \quad \cos(\nu, z) = \frac{z}{r'_2}. \quad (4)$$

From (2) and (3),

$$p = \frac{RT}{M} (c_2 - c'_2), \quad p' = -\frac{2\gamma}{r'_2}, \quad (5)$$

which mean that the components of the normal force at any point of the sphere are

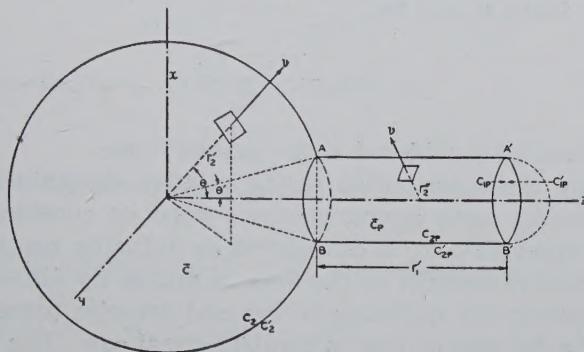


FIGURE 1

$$X_v = \left[\frac{RT}{M} (c_2 - c'_{2'}) - \frac{2\gamma}{r'_2} \right] \frac{x}{r'_2}, \dots, \quad (6)$$

the other two components being derived by multiplying the bracketed expression with the proper direction cosine. Substituting these in (1) we have for the contribution of the spherical portion, the expression,

$$\begin{aligned} I_s = & -\frac{3RT\mu}{2M} \int_S \frac{c_2}{r'_2} [z^2 - \frac{1}{2}(x^2 + y^2)] dS \\ & + \int_S \left[\frac{RT}{M} (c_2 - c'_{2'}) - \frac{2\gamma}{r'_2} \right] \frac{1}{r'_2} [z^2 - \frac{1}{2}(x^2 + y^2)] dS. \end{aligned} \quad (7)$$

This integral may be evaluated by using spherical coordinates and turns out to be

$$I_s = \pi r'^{2}_2 \cos \theta' \sin^2 \theta' \left[\frac{3RT\mu}{2M} - \frac{RT}{M} (c_2 - c'_{2'}) + \frac{2\gamma}{r'_2} \right]. \quad (8)$$

Similarly by considering the cylindrical portion we have

$$I_c = \pi r''^{2}_2 r'_1 \left[\frac{3RT\mu}{2M} c_{2p} - \frac{RT}{M} (c_{2p} - c'_{2p}) + \frac{\gamma}{r''_2} \right]. \quad (9)$$

At this point, it should be indicated that the assumption has been made that c_{2p} remains constant over the entire length of the cylindrical surface. If we consider a cell like some of the yeasts which have very long protrusions, this would be a close approximation, especially if production of the substance still goes on in the protrusion. How-

ever, for short lengths as in pseudopods in amoebae, this approximation may be doubtful. In this case, an expression which should be closer to the truth would be,

$$c_{2p} = c_2 - \frac{c_2 - c_{1p}}{r'_1} z \quad (10)$$

but this will not be considered at the present time.

In finding the contribution to the relative elongation of the end of the protrusion, some approximations must be considered for convenience. If the substance is considered as diffusing across the end in a direction always parallel to the axis, it makes no difference mathematically whether the diffusion forces and osmotic pressure are calculated over a flat end or over a hemispherical cap. The contribution from surface tension must be considered over a hemispherical cap mathematically. That the diffusion will not behave in this manner is rather obvious, since the substance will diffuse or flow normally across the boundary, but the approximation will be reasonably close under the simplifying assumptions made. If it is assumed that c_{1p} is a constant over the spherical cap, the second method will be approximated.

The calculations lead to

$$I_e = \pi r''_2^2 (r'_1 + r'_2 \cos \theta') \left[-\frac{3RT\mu}{2M} c_{1p} + \frac{RT}{M} (c_{1p} - c'_{1p}) - \frac{2\gamma}{r''_2} \right] \quad (11)$$

and we are now in a position to examine the relative elongation.

Substituting (8) (9) and (11) for the expression in braces of (1), we have, after some simplification,

$$\begin{aligned} \frac{1}{L_z} \frac{dL_z}{dt} &= \frac{\pi RT\mu}{2\eta VM} \left\{ c_2 r'^2_2 \cos \theta' \sin^2 \theta' + c_{2p} r''_2^2 r'_1 - c_{1p} r''_2^2 (r'_1 \right. \\ &\quad \left. + r'_2 \cos \theta') \right. \\ &\quad \left. + \frac{2\gamma M}{3RT\mu} [2r'^2_2 \cos \theta' \sin^2 \theta' + r'_1 r''_2 - 2r''_2 (r'_1 + r'_2 \cos \theta')] \right\} \quad (12) \\ &\quad - \frac{2}{3\mu} \left[(c_2 - c'_2) r'^2_2 \cos \theta' \sin^2 \theta' + (c_{2p} - c'_{2p}) r''_2^2 r'_1 \right. \\ &\quad \left. - (c_{1p} - c'_{1p}) r''_2^2 (r'_1 + r'_2 \cos \theta') \right\} \end{aligned}$$

which gives the relative rate of increase of length in the z direction. Of course, in this problem, there will be a contraction in the other two directions at right angles to this direction under the assumptions of cylindrical symmetry.

To simplify the expression let

$$A = \frac{2M\gamma}{3RT\mu}; \quad B = \frac{\pi RT\mu}{2\eta VM}; \quad \alpha = \frac{2}{3\mu} \quad (13)$$

and from the diagram, Figure 1, clearly,

$$r''_2 = r'_2 \sin \theta'. \quad (14)$$

The relative elongation then becomes

$$\begin{aligned} \frac{1}{L_z} \frac{dL_z}{dt} &= B r'_2 \sin \theta' \{ -A [r'_1 + 2r'_2 (1 - \sin \theta') \cos \theta'] \\ &+ r'_2 \sin \theta' [(c_2 - c_{1p}) r'_2 \cos \theta' - \alpha (c_2 - c'_2 - c_{1p} + c'_{1p}) \\ &\times r'_2 \cos \theta' + (c_{2p} - c_{1p}) r'_1 - \alpha (c_{2p} - c'_{2p} - c_{1p} + c'_{1p}) r'_1] \}. \end{aligned} \quad (15)$$

The terms involving α arise from the contribution of osmotic pressure, and if the enclosing membrane has infinite permeability (h) these will vanish.

Elongation will take place when the right hand side of (15) is positive, and for equilibrium conditions it will be close to zero. Under the simplifying assumptions of infinite permeability, protrusion will occur when

$$\begin{aligned} r'^2_2 (c_2 - c_{1p}) \sin \theta' \cos \theta' - A r'_1 \\ + [(c_{2p} - c_{1p}) r'_1 \sin \theta' - 2A (1 - \sin \theta') \cos \theta'] r'_2 > 0. \end{aligned} \quad (16)$$

Physical considerations of the mechanism of diffusion require that, for a cell which is producing a substance,

$$c_2 > c_{2p} > c_{1p}, \quad (17)$$

and all quantities in parentheses involving the concentrations be positive.

Hence (16) imposes immediately the restriction that r'_2 must be greater than the single positive zero of the quadratic in r'_2 , and so determines a lower bound for the size of the cell in terms of r'_1 , θ' and the concentrations. It is more useful, however, to consider the restrictions imposed upon the other parameters, and so we arrange (16) in the form

$$\begin{aligned} (r'_1 + r'_2 \cos \theta') [A - r'_2 (c_{2p} - c_{1p}) \sin \theta'] \\ < r'_2 \cos \theta' [A (2 \sin \theta' - 1) + r'_2 \sin \theta' (c_2 - c_{2p})]. \end{aligned} \quad (18)$$

We may consider separately the following possibilities:

I. $A - r'_2(c_{2p} - c_{1p}) \sin \theta'$
 $> A(2 \sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{2p}) > 0;$

II. $0 > A - r'_2(c_{2p} - c_{1p}) \sin \theta'$
 $> A(2 \sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{2p});$

III. $A(2 \sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{2p})$
 $> A - r'_2(c_{2p} - c_{1p}) \sin \theta' > 0;$

IV. $0 > A(2 \sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{2p})$
 $> A - r'_2(c_{2p} - c_{1p}) \sin \theta';$

V. $A - r'_2(c_{2p} - c_{1p}) \sin \theta'$
 $> 0 > A(2 \sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{2p});$

VI. $A(2 \sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{2p})$
 $> 0 > A - r'_2(c_{2p} - c_{1p}) \sin \theta'.$

Cases I and V cannot satisfy (18) for any positive value for r'_1 and consequently represent conditions of insufficient production and no consequent growth. Cases IV and VI will meet the requirements for any value of r'_1 , and case II also, provided r'_1 is sufficiently large. These three cases represent necessary conditions for continued growth. In contrast to the abundance of these, case III is the only one which establishes an upper limit for the length, r'_1 .

By means of (18) and (19) various relations can be established among the parameters. We suppose the cell to be producing the diffusing substance so that (17) holds. All of the conditions, II, IV, VI and III, require

$$c_2 > c_{1p} \quad (20)$$

automatically, but if in addition $c_2 > c_{2p}$ they also demand that

$$\sin \theta_1 < \frac{1}{2} \quad (21)$$

or from (14)

$$r''_2 < \frac{1}{2}r'_2. \quad (22)$$

In case II under these conditions, it follows that

$$\frac{\frac{r'_2 \cos \theta' [2A(1 - \sin \theta') - r'_2 \sin \theta'(c_2 - c_{1p})]}{r'_2 \sin \theta'(c_{2p} - c_{1p}) - A} < r'_1 < \infty}{\frac{A}{r'_2(c_{2p} - c_{1p})} \leq \sin \theta' \leq \frac{2A + r'_2(c_2 - c_{1p})}{2A + r'_2(c_2 - c_{1p})}} \quad (23)$$

$$c_{2p} > \frac{c_2 + (1 - 2 \sin \theta') c_{1p}}{2(1 - \sin \theta')} > \frac{c_2 + c_{1p}}{2}.$$

Case IV similarly gives

$$\begin{aligned} 0 < r'_1 < \infty \\ \sin \theta' &> \frac{2A}{2A + r'_2(c_2 - c_{1p})} \\ c_{2p} &> \frac{c_2 + (1 - 2 \sin \theta') c_{1p}}{2(1 - \sin \theta')}. \end{aligned} \quad (24)$$

The middle inequality together with (21) requires

$$r'_2 > \frac{A}{c_2 - c_{1p}}. \quad (25)$$

The only difference between cases IV and VI involves the concentration c_{2p} which is limited in range such that

$$c_2 + \frac{A(2 \sin \theta' - 1)}{r'_2 \sin \theta'} > c_{2p} > c_{1p} + \frac{A}{r'_2 \sin \theta'}. \quad (26)$$

The final case to be considered is that permitting only limited growth, case III, which gives the relations

$$\begin{aligned} 0 < r'_1 &< \frac{r'_2 \cos \theta' [2A(\sin \theta' - 1) + r'_2 \sin \theta'(c_2 - c_{1p})]}{A - r'_2 \sin \theta'(c_{2p} - c_{1p})} \\ \sin \theta' &> \frac{2A}{2A + r'_2(c_2 - c_{1p})} \\ c_{2p} &< \frac{c_2 + (1 - 2 \sin \theta') c_{1p}}{2(1 - \sin \theta')}. \end{aligned} \quad (27)$$

These relations are necessary conditions for growth to occur. They all seem to be very similar in the terms involved and the various dependencies. The concentration c_{2p} on the sides of the protrusion will be directly dependent on the rate of production in the protrusion, and it will increase as the production increases, particularly when the protrusion is very long, or relatively narrow so that diffusion from the main cell body becomes relatively unimportant in the protrusion except in the neighborhood of the base. For this reason, the relations involving c_{2p} may give some indication as to the extent of activity in the protrusion.

With this in mind, one would expect that when only limited growth is permitted, the activity in the protrusion would be a minimum, whereas higher activities would cause the growth to continue

indefinitely. Of the cases allowing this, II permits the narrowest protrusion, but because of the lower limit for r'_1 , the parameters must be adjusted so that one of the other cases applies first, whereupon case II may be followed. It might seem apparent that with sufficiently large cells which are following this pattern, a point might be reached where the protrusion had vanishing diameter. This is, however, not the case, for by considering (14) and large r'_2 we find

$$r''_2 = \frac{2A}{c_2 - c_{1p}}, \quad c_{2p} = \frac{c_2 + c_{1p}}{2} \quad (28)$$

which gives a value of the radius of the protrusion depending only on the surface tension constant and the concentrations.

In the calculations, no assumption has been made of constant volume, and this picture requires that fluid diffuse into the cell sufficiently fast to permit growth, and the phenomena are, therefore, only long time ones to which this analysis would apply. This approach gives considerable simplification in the use and interpretation of Betti's formula, since r'_2 can be considered constant. This means that L_z will be a linear function of r'_1 only and the relative elongation rate can be thought of as involving only this quantity as changing with time. Also lateral contractions which are implicit with the assumption of constant volume do not enter.

If constant volume is assumed, which includes the more general case, L_z would be a function of r'_2 and r'_1 and from physical considerations, only limited growth would be possible since the main cell body would decrease in size as growth progressed. Also lateral contractions should properly be calculated. This extended problem might well apply to numerous cells and growths which cannot be treated in this simplified discussion, such as amoeboid movements. The present paper may have applications in yeast and nerve growths.

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A THEORY OF ELECTRICAL POLARITY IN CELLS: II

ROBERT R. WILLIAMSON
THE UNIVERSITY OF CHICAGO

Orders of magnitude and relations of the constants in the equations of the polar cell are discussed. Some considerations on the mechanism of polarity are presented, and a more general mechanism discussed. It is shown that polarity can exist without catalysis, either stimulating or inhibiting.

In a preceding paper (Williamson and Bloch, 1942) equations were derived determining the polarity of a cell maintained by diffusion and electrical forces. The diffusion forces acted in two ways, i.e.; (1) they acted directly on the catalyst particles to produce a polarity if the particles inhibited the reaction responsible for the diffusion forces, or to prevent a polarity if the particles promoted the reaction, and (2) they separated ions of opposite charge produced by the reaction by a differential in diffusion rates. The second action leads to an electrical polarity of the cell which influences the distribution of the colloidal particles if the catalyst particle has a charge. In the case of an inhibitory catalyst the diffusion forces of the first kind always tend to establish a polarity, while in the case of a promoting catalyst they will oppose a polarity. The electrical forces will either aid or oppose a polarity depending on the signs of $(D_+ - D_-)$ and v (the charge born by the catalyst.)

The equations determining polarity are (Williamson and Bloch, 1942)

$$n_1 - n_2 = y = 2n \tanh \frac{My}{2}, \quad (1)$$

$$M = \gamma \zeta a + \frac{\beta \zeta a}{kT} - \frac{\beta v}{RT},$$

$$Q_1 = Q_0 - a n_1,$$

$$Q_2 = Q_0 - a n_2,$$

$$\gamma = \frac{3Nv}{2}, \quad (2)$$

$$\zeta = \frac{r_0^2}{a} \left(\frac{1}{D_+} + \frac{1}{D_-} \right), \quad \xi = \frac{r_0^2}{a} \left(\frac{1}{D_+} - \frac{1}{D_-} \right),$$

$$\beta = \frac{.56 \pi r_0^2 N \nu \varepsilon^2}{K}.$$

If we let $r_0 = 10^{-3}$ cm, $r_v = 10^{-5}$ cm to 10^{-8} cm, $D_+ = 10^{-7}$ $\text{cm}^2 \text{ sec}^{-1}$, $D_- = 10^{-8}$ $\text{cm}^2 \text{ sec}^{-1}$, $K = 80$ we obtain as the upper and lower limits of M

$$M < 4 \cdot 10^{11}a + 5 \cdot 10^{13}a - 1.7 \cdot 10^{-4}$$

$$< 5 \cdot 10^{13}a - 1.7 \cdot 10^{-4},$$

$$M > 4 \cdot 10^2a - 5 \cdot 10^{15}a - 1.7 \cdot 10^{-9}$$

$$> 5 \cdot 10^{13}a.$$

Thus we see that M may cover a very wide range.

If $|My|$ is large

$$y = 2n \frac{e^{\frac{My}{2}} - e^{-\frac{My}{2}}}{e^{\frac{My}{2}} + e^{-\frac{My}{2}}} \rightarrow \pm 2n;$$

i.e., either

$$n_1 = 2n \text{ and } n_2 = 0 \text{ when } M > 0,$$

or

$$n_2 = 2n \text{ and } n_1 = 0 \text{ when } M < 0.$$

When My is small we can expand $\tanh My/2$, and take only the first two terms. This gives a better approximation for $|My| \geq 1$ than the first three terms, and a good approximation for $|My| < 2$.

The equation then has the stable roots

$$y = \pm \frac{2}{M} \left(\frac{3nM - 3}{nM} \right)^{\frac{1}{2}},$$

and the unstable root $y = 0$. When $a > 0$ it is necessary that

$$Q_0 \geq an_1, \quad Q_0 \geq an_2$$

to prevent negative reactions. Then

$$Q_0 \geq a \frac{n_1 + n_2}{2} = an.$$

The non-null real roots will exist only if $nM > 1$. This is equivalent

to the condition

$$\frac{d}{dy} \tanh \frac{My}{2} \Big|_0 > \frac{1}{2n},$$

which is geometrically necessary, as seen by examination of the graphs of $\tanh My/2$.

If we neglect $\beta r/RT$, $M = aB$, and the upper and lower limits indicate

$$-5 \cdot 10^{13} \leq B = \gamma \zeta + \frac{\beta \xi}{kT} \leq 5 \cdot 10^{13}.$$

If we make $My < 2$ so that we can use the expansion, we have

$$Q_0 > an > \frac{1}{B} > \frac{a(n_1 - n_2)}{2}.$$

Thus if $Q_0 \propto 10^{-7}$ moles $\text{cm}^{-3} \text{ sec}^{-1}$, then $an < 10^{-7}$ moles $\text{cm}^{-3} \text{ sec}^{-1}$. Furthermore, since the volume of the cell is of the order of $4 \cdot 10^{-9} \text{ cm}^3$, and as there must be of the order of 10 to 1000 particles in the cell if the distribution is to have any statistical uniformity, we have

$$n \propto \frac{10}{4 \cdot 10^{-9}} \text{ to } \frac{10^3}{4 \cdot 10^{-9}},$$

or $n \propto 2.5 \cdot 10^9$ to $2.5 \cdot 10^{11}$ particles cm^{-3} at least. This corresponds, if each particle bears one molecule of catalyst, to a solution of the catalyst of $4 \cdot 10^{-12}$ to $4 \cdot 10^{-10}$ moles liter $^{-1}$. This is at the lower limit of dilution of the most potent biologicals, and therefore we would expect either a higher n or more catalyst molecules per particle. There is another factor, however, which alters these considerations. The volume of the cell is $4\pi r_0^3/3$, while the volume of each particle is $4\pi r_v^3/3$. The relative volume of active protoplasm left is then $1 - 4\pi nr_v^3/3$. We must assume then that the catalyst concentration is, in terms of active protoplasm

$$C_c = \frac{n}{N} \cdot \frac{10^3}{1 - 4\pi nr_v^3/3} \text{ moles/liter.}$$

However, because the catalyst molecule is screened by the inert mass of the particle on one side, the effective concentration is roughly only one-half of this since only half as many molecules can get to the catalyst in a given time interval as when the catalyst is freely dissolved in solution.

If we revise the derivation consistently with the assumption that

the particles are impenetrable to the metabolites, we must introduce two new changes in the original derivation. The diffusion coefficients of the metabolites will be altered by the presence of these particles. Einstein (1906) has shown that a suspension of rigid spheres of uniform size whose common radius is greatly exceeded by the mean distance between the particles and the smallest dimension of the shearing liquid, has a viscosity,

$$\eta_i = \eta_0(1 + 2.5vn_i),$$

where vn_i is the fraction of the volume occupied by the dispersed particles and η_0 is the viscosity of the fluid alone. Also Smoluchowski (1916) has shown that if the particles carry an electric charge the viscosity is further increased by an electro-viscous effect thus

$$\eta_i = \eta_0 \left\{ 1 + 2.5n_i v \left[1 + \frac{1}{\lambda_e \eta_0} \left(\frac{K \phi}{2 \pi r_v} \right) \right] \right\},$$

where

λ_e = specific conductivity,

K = dielectric constant,

ϕ = electrokinetic potential.

If we let

$$\alpha = 2.5 \left[1 + \frac{1}{\lambda_e \eta_0} \left(\frac{K \phi}{2 \pi r_v} \right) \right],$$

$$\eta_i = \eta_0(1 + \alpha vn_i).$$

Einstein's expression for the diffusion coefficient is

$$D = \frac{kT}{6 \pi \eta r}.$$

If we introduce the above and expand we have

$$\begin{aligned} D_i &= \frac{kT}{6 \pi \eta_0(1 + \alpha vn_i)r} = \frac{kT}{6 \pi \eta_0 r} (1 - \alpha vn_i) \\ &= D_0(1 - \alpha vn_i). \end{aligned}$$

Because of the many crude assumptions the above can be considered only a first approximation.

The second change required in the original derivation is the following. If Q_0 is the production rate of a metabolite in protoplasm without granules, we have, for protoplasm containing granules,

$$Q_i = Q_0(1 - vn_i),$$

and if the particles bear a catalyst,

$$\begin{aligned} Q_i &= Q_0(1 - vn_i) + bn_i = Q_0 - (Q_0v - b)n_i \\ &= Q_0 - an_i, \end{aligned}$$

where

$$a = Q_0v - b.$$

This equation is identical in form with the previous equation, but has a more general physical significance. It now becomes apparent that a polarity can occur even without the catalyst. We should expect self regulating polarities resulting from this mechanism in cells having no structure more specific than some granules, or a vacuole.

The solution of the equations resulting becomes extremely involved because of the non-linearities introduced. They must reduce to the equations of Williamson and Bloch (1942) as a first approximation, however, and for the preliminary applications to biological problems the older equations will do very well.

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GREEN'S FUNCTIONS IN BIOLOGICAL POTENTIAL PROBLEMS

ALVIN M. WEINBERG
THE UNIVERSITY OF CHICAGO

Electrical potential problems encountered in biology differ from those usually considered in electrical theory first, because the membranes of tissues satisfy a non-linear relation between current flow and polarization, and second, because the interior of the tissues are not equipotentials. A Green's function suitable for discussing such problems is defined, and a cylindrical illustration of such a function is discussed.

Potential problems arising in the electrophysiology of nerve and muscle are of a type not usually encountered in electrical theory for two reasons: first, because of its finite internal conductivity, the interior of an active or injured fiber is not strictly equipotential; second, because the membrane resistance is generally a function of the membrane current flow, (Cole and Curtis, 1941) the boundary conditions are non-linear. In the present note a Green's function suitable for the solution of such problems will be defined and a cylindrical illustration due to H. Weber will be discussed. The results are at present primarily of mathematical interest, and are rather closely related to some results first stated by H. Helmholtz (1853). It is hoped that they may constitute a ground work for future attempts to analyze bioelectric potentials by the methods of potential theory.

1. The Green's function.

Suppose u_e and u_i are the steady state potentials outside and inside a tissue covered by a closed polarized membrane, S (Figure 1).

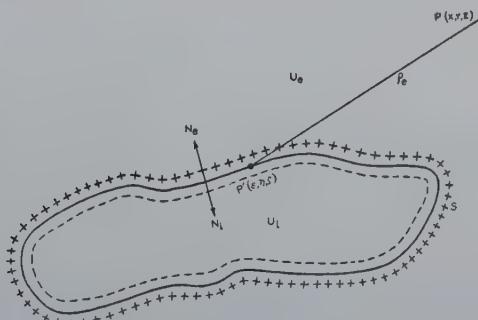


FIGURE 1

Then u_e and u_i are harmonic functions which satisfy, in general, a non-linear boundary condition at the membrane:

$$k_e \frac{\partial u_e}{\partial n_e} = -k_i \frac{\partial u_i}{\partial n_i} = F(u_e - u_i) \text{ on } S_1, \quad (1)$$

or

$$u_e - u_i = \Phi_e \left(\frac{\partial u_e}{\partial n_i} \right) = \Phi_i \left(\frac{\partial u_i}{\partial n_i} \right),$$

where k_e and k_i are the conductivities of the external and internal media, n_e and n_i are the outwardly and inwardly drawn normals on S , and $F(u_e - u_i)$ is some function of the membrane potential difference which determines the membrane current flow. The exact form of F has been determined experimentally by K. S. Cole and H. J. Curtis (1941) in the squid giant axon. Prior to this work, most writers on the theory of the propagated impulse had assumed a piece-wise linear relation between the membrane current and the membrane potential difference of the general form

$$F(u_e - u_i) = \frac{k_e}{h}(u_e - u_i - E) \quad (2)$$

where E , the "membrane E.M.F.", is constant except in active regions, where it is zero (Rushton, 1937). The constant h is the ratio of the external conductivity to the membrane conductivity per square centimeter; it is a constant only for very small membrane current density. To complete the specification of the problem, we shall assume either that the vessel, V , in which the tissue is immersed is an insulator, in which case

$$\frac{\partial u_e}{\partial n_e} = 0 \quad \text{on } V, \quad (3)$$

or that it is a "diffuse ground", in which case

$$u_e = 0 \quad \text{on } V. \quad (4)$$

Both of these experimental situations arise in practice.

Consider an exterior point $P(x,y,z)$ from which the distance ρ_e to a variable point $P'(\xi, \eta, \zeta)$ is

$$\rho_e^2 = (\xi - x)^2 + (\eta - y)^2 + (\zeta - z)^2. \quad (5)$$

The reciprocal distance $1/\rho_e$ has a pole in the exterior at the point P , while it is a continuous function everywhere in the interior. Conse-

quently from Green's theorem

$$\begin{aligned} u_e(x,y,z) = & \frac{1}{4\pi} \int \int_s \left[\frac{1}{\rho_e} \frac{\partial u_e}{\partial n_i} - u_e \frac{\partial(1/\rho_e)}{\partial n_i} \right] d\omega \\ & + \frac{1}{4\pi} \int \int_v \left[\frac{1}{\rho_e} \frac{\partial u_e}{\partial n_e} - u_e \frac{\partial(1/\rho_e)}{\partial n_e} \right] d\omega', \end{aligned} \quad (6)$$

and

$$0 = \frac{k_i}{4\pi k_e} \int \int_s \left[\frac{1}{\rho_e} \frac{\partial u_i}{\partial n_e} - u_i \frac{\partial(1/\rho_e)}{\partial n_e} \right] d\omega, \quad (7)$$

where ω and ω' are surface elements on S and V respectively.

Let us now introduce two harmonic functions, H_e defined in the exterior, and H_i defined in the interior, which have the properties:

$$\frac{\partial G_e^e}{\partial n_e} = -\frac{k_i}{k_e} \frac{\partial G_i^e}{\partial n_i} = (G_e^e - G_i^e) \quad \text{on } S, \quad (8)$$

$$G_e^e = 0 \text{ if } u_e = 0; \quad \text{or} \quad \frac{\partial G_e^e}{\partial n_i} = \frac{4\pi}{v} \text{ if } \frac{\partial u_e}{\partial n_e} = 0 \quad \text{on } V, \quad (9)$$

where v is the surface area of the insulating vessel (cf. Kellogg, 1929, p. 246) and

$$\begin{aligned} G_e^e(x, y, z; \xi, \eta, \zeta) &\equiv 1/\rho_e + H_e(\xi, \eta, \zeta); \\ &\quad \left. \begin{aligned} (x, y, z) \\ (\xi, \eta, \zeta) \end{aligned} \right\} \text{in exterior}, \end{aligned} \quad (10)$$

and

$$\begin{aligned} G_i^e(x, y, z; \xi, \eta, \zeta) &\equiv 1/\rho_e + H_i(\xi, \eta, \zeta). \\ &\quad \left. \begin{aligned} (x, y, z) \\ (\xi, \eta, \zeta) \end{aligned} \right\} \text{in exterior}, \\ &\quad \text{in interior}. \end{aligned} \quad (11)$$

Then, since H_e and H_i are both harmonic,

$$\begin{aligned} 0 = & \frac{1}{4\pi} \int \int_s \left[H_e \frac{\partial u_e}{\partial n_i} - u_e \frac{\partial H_e}{\partial n_i} \right] d\omega \\ & + \frac{1}{4\pi} \int \int_v \left[H_e \frac{\partial u_e}{\partial n_e} - u_e \frac{\partial H_e}{\partial n_e} \right] d\omega', \end{aligned} \quad (12)$$

and

$$0 = \frac{k_i}{4\pi k_e} \int \int_s \left[H_i \frac{\partial u_i}{\partial n_e} - u_i \frac{\partial H_i}{\partial n_e} \right] d\omega. \quad (13)$$

If we add equations (6), (7), (12) and (13), and use the conditions (8), (10) and (11), we find

$$\begin{aligned} u_e(x, y, z) = & \frac{1}{4\pi} \int_S \int \left[G_{e^e} \frac{\partial u_i}{\partial n_e} + \frac{k_i}{k_e} G_{i^e} \frac{\partial u_i}{\partial n_e} \right. \\ & \left. - (G_{i^e} - G_{e^e})(u_e - u_i) \right] d\omega \quad (14) \\ & + \frac{1}{4\pi} \int_V \int \left[G_{e^e} \frac{\partial u_e}{\partial n_e} - u_e \frac{\partial G_{e^e}}{\partial n_e} \right] d\omega'. \end{aligned}$$

The last integral vanishes if the diffuse ground is used; otherwise (insulating vessel) its value is

$$\bar{u}_{ev} = \frac{1}{V} \int \int u_e(\xi, \eta, \zeta) d\omega'; \quad (15)$$

this represents the average value of the potential over the containing vessel.

The first integral may be simplified by substituting equations (1) and (8) and using the fact that $\partial/\partial n_i = -\partial/\partial n_e$. The final result is, for a diffuse ground boundary condition

$$\begin{aligned} u_e(x, y, z) = & \frac{1}{4\pi} \int_S \int \left[\frac{\partial u_e}{\partial n_i} + \Phi_e \left(\frac{\partial u_e}{\partial n_i} \right) \right] \\ & \times [G_{e^e}(x, y, z; \xi, \eta, \zeta) - G_{i^e}(x, y, z; \xi, \eta, \zeta)] d\omega, \quad (16) \end{aligned}$$

and for an insulating vessel boundary condition

$$\begin{aligned} u_e(x, y, z) = & \frac{1}{4\pi} \int_S \int \left[\frac{\partial u_e}{\partial n_i} + \Phi_e \left(\frac{\partial u_e}{\partial n_i} \right) \right] [G_{e^e}(x, y, z; \xi, \eta, \zeta) \\ & - G_{i^e}(x, y, z; \xi, \eta, \zeta)] d\omega + \bar{u}_{ev}. \quad (17) \end{aligned}$$

The additive constant \bar{u}_{ev} in the insulating vessel case is required since only normal derivatives and differences between u_e and u_i , neither of which can determine a zero of potential, enter in the specification of the problem (cf. Kellogg, 1929, p. 246). In the diffuse ground case ($\bar{u}_{ev} = 0$), the zero of potential is determined uniquely by the fact that the vessel is assumed to be a perfect conductor at ground potential.

Expressions analogous to equations (16) and (17) can be given

for the interior potential; for example, in the insulating vessel case,

$$u_i(x, y, z) = \frac{k_e}{4\pi k_i} \int_s \int \left[\frac{\partial u_i}{\partial n_e} + \Phi_i \left(\frac{\partial u_i}{\partial n_i} \right) \right] [G_i^i - G_e^i] d\omega + \bar{u}_{ev}$$

where the G_i^i and G_e^i are interior Green's functions defined over the following ranges:

$$\begin{aligned} G_i^i(x, y, z; \xi, \eta, \zeta) &\quad \left. \begin{aligned} (x, y, z) \\ (\xi, \eta, \zeta) \end{aligned} \right\} && \text{in interior,} \\ G_e^i(x, y, z; \xi, \eta, \zeta) &\quad \left. \begin{aligned} (x, y, z) \\ (\xi, \eta, \zeta) \end{aligned} \right\} && \text{in interior,} \\ && & \text{in exterior,} \end{aligned}$$

and satisfying equations (8) and (9). In biological applications, the interior problem is usually of less interest than the exterior problem. This is because the volume of many irritable tissues (e.g. individual nerve fibers) is so small that accurate interior measurements are very difficult (see, however, Graham, Carlson, and Gerard, 1942).

As an example of the sort of biological conclusion which can be drawn from equations (16) and (17), we may prove the rather self-evident statement: *the external potential of a resting tissue is everywhere constant ($= \bar{u}_{ev}$)*. For, by definition, in a resting tissue the membrane current, $\partial u_e / \partial n_i$, is identically zero. Consequently, $\Phi_e(0)$ is identically equal to E , the resting membrane E.M.F. (a constant), over the tissue surface, and, from equations (17) and (18)

$$\begin{aligned} u_e(x, y, z) &= \frac{-k_i E}{4\pi k_e} \int_s \int \frac{\partial G_i^e}{\partial n_i} d\omega + \bar{u}_{ev} \\ &= \bar{u}_{ev} \end{aligned}$$

since G_i^e is harmonic in the interior and the surface integral over a closed surface of the normal derivative of a harmonic function is zero by Gauss's theorem.

It may be mentioned that practically all of the discussion of the "dipole" hypothesis (Wilson, McCleod and Barker, 1933) can be put on a rigorous mathematical basis by application of the formulae of this section.

2. Weber's two-phase kernleiter.¹

¹ Weber's one-phase kernleiter, in which the interior is a perfect conductor, has been considered before (Weinberg, 1941). The sign of h in the discussion of the infinite external medium should be reversed in that paper.

An example of a Green's function of the type discussed in 1 was given by H. Weber (1873) in discussing the stationary current flow around an infinite cylindrical kernleiter (radius b) surrounded by a concentric glass cylinder of radius $a (> b)$, the intervening medium being filled with an electrolyte. The interior and exterior Green's functions are defined by

$$\frac{\partial^2 G_e^{e,i}}{\partial r'^2} + \frac{1}{r'} \frac{\partial G_e^{e,i}}{\partial r'} + \frac{\partial^2 G_e^{e,i}}{\partial \phi'^2} + \frac{\partial^2 G_e^{e,i}}{\partial z'^2} = 0 \quad (b < r' < a),$$

$$\frac{\partial^2 G_i^{e,i}}{\partial r'^2} + \frac{1}{r'} \frac{\partial G_i^{e,i}}{\partial r'} + \frac{1}{r'^2} \frac{\partial^2 G_i^{e,i}}{\partial \phi'^2} + \frac{\partial^2 G_i^{e,i}}{\partial z'^2} = 0 \quad (0 < r' < b),$$

with the following boundary conditions:

$$G_{e,i}^e = G_{e,i}^i = 0 \quad \text{at } z' = \infty; \quad \frac{\partial G_{e,i}^{e,i}}{\partial r'} = 0 \quad \text{at } r' = b,$$

$$h \frac{\partial G_{e,i}^{e,i}}{\partial r'} = h \frac{k_i}{k_e} \frac{\partial G_i^{e,i}}{\partial r'} = G_{e,i}^{e,i} - G_i^{e,i} \quad \text{at } r' = a,$$

$$\frac{\partial G_{e,i}^{e,i}}{\partial z'} = \frac{1}{k_e} \delta(r - r') \delta(\phi - \phi') \quad \text{at } z = z',$$

$$\frac{\partial G_i^{e,i}}{\partial z'} = \frac{1}{k_i} \delta(r - r') \delta(\phi - \phi') \quad \text{at } z = z',$$

where r' , ϕ' , z' are cylindrical coordinates of the field point, r , ϕ , z of the source point, superscripts refer to the position of the source point, δ is the Dirac delta function, and h is the ratio of external to membrane conductivity per square centimeter. The solution of this problem as given by H. Weber is

$$b < r' < a \quad G_e^e(r, \phi, z, r', \phi', z')$$

$$b < r < a$$

$$= \frac{1}{\pi^2 k_e^2} \sum_{n=0}^{\infty} \sum_{\theta} \frac{\varepsilon_n}{\theta N_{n,\theta}} f_n(r', \theta) f_n(r, \theta)$$

$$\times \cos n(\phi - \phi') e^{-\theta|z-z'|}$$

$$0 < r' < b$$

$$b < r < a \quad G_i^e(r, \phi, z; r', \phi', z')$$

$$= \frac{1}{\pi^2 k_e k_i} \sum_{n=0}^{n=\infty} \sum_{\theta} \frac{\varepsilon_n}{\theta N_{n,\theta}} f_n(r, \theta) \phi_n(r', \theta)$$

$$\times \cos n(\phi - \phi') e^{-\theta|z-z'|}$$

and

$$b < r' < a$$

$$G_e^i(r, \phi, z; r', \phi', z')$$

$$0 < r < b$$

$$= \frac{1}{\pi^2 k_e k_i} \sum_{n=0}^{n=\infty} \sum_{\theta} \frac{\varepsilon_n}{\theta N_{n,\theta}} \phi_n(r, \theta) f_n(r', \theta)$$

$$\times \cos n(\phi - \phi') e^{-\theta|z-z'|}$$

$$0 < r' < b$$

$$G_i^i(r, \phi, z; r', \phi', z')$$

$$0 < r < b$$

$$= \frac{1}{\pi^2 k_i^2} \sum_{n=0}^{n=\infty} \sum_{\theta} \frac{\varepsilon_n}{\theta N_{n,\theta}} \phi_n(r', \theta) \phi_n(r, \theta)$$

$$\times \cos n(\phi - \phi') e^{-\theta|z-z'|}$$

where

$$f_n(r, \theta) = J_n(\theta r) Y_n'(\theta a) - Y_n(\theta r) J_n'(\theta a),$$

$$\phi_n(r, \theta) = \alpha J_n(\theta r),$$

$$\alpha = k_e [J_n(\theta b) Y_n'(\theta a) - Y_n(\theta b) J_n'(\theta a)] / [h k_i J_n'(\theta b) + k_e J_n(\theta b)],$$

$$N_{n,\theta} = \frac{1}{k_i} \int_0^b r \phi_n^2(\theta r) dr + \frac{1}{k_e} \int_b^a r f_n^2(\theta r) dr,$$

$$\varepsilon_0 = 1, \quad \varepsilon_1 = \varepsilon_2 \dots = 2,$$

and the characteristic values θ are roots of

$$h \theta k_i = k_i [J_n(\theta b) Y_n'(\theta a) - Y_n(\theta b) J_n'(\theta a)] / [J_n'(\theta b) Y_n'(\theta a) - Y_n(\theta b) J_n'(\theta a)] - k_e J_n(\theta b) / J_n'(\theta b).$$

The symbols J_n and Y_n stand for Bessel functions of the first and second kinds respectively; primes represent derivatives.

The characteristic equation reduces to

$$h \theta = [J_n(\theta b) Y_n'(\theta a) - Y_n(\theta b) J_n'(\theta a)] / [J_n'(\theta b) Y_n'(\theta a) - Y_n(\theta b) J_n'(\theta a)]$$

when $k_i > k_e$; this case was discussed in a previous paper. On the

other hand, when $k_e > k_i$,

$$h \theta \frac{k_i}{k_e} J'_n(\theta b) + J_n(\theta b) = 0.$$

this is the characteristic equation for an interior cylindrical problem, and its roots have been tabulated (Carslaw, p. 321).

An application of this Green's function which is of some biological interest is the following: consider an infinitely long kernleiter whose surface carries a uniform polarization, E , from $z = 0$ to $z = \infty$, and no polarization from $z = -\infty$ to $z = 0$. Such a partially depolarized kernleiter may be taken to represent a nerve fiber in which an injury current is flowing. The boundary conditions at $r = a$ are of the form

$$\begin{aligned} k_e \frac{\partial u_e}{\partial n_e} &= -k_i \frac{\partial u_i}{\partial n_i} = \frac{k_e}{h} (u_e - u_i - E) & z > 0, \\ &= \frac{k_e}{h} (u_e - u_i) & z < 0. \end{aligned}$$

To determine the external potential we may substitute these conditions into equation (14); we obtain

$$\begin{aligned} u_e(r, \phi, z) &= \frac{aE}{4\pi} \int_0^\infty \int_0^{2\pi} [G_{e^e}(r, \phi, z; a, \phi', z') \\ &\quad - G_{i^e}(r, \phi, z; a, \phi', z')] d\theta' dz'. \end{aligned}$$

In the integration all Bessel functions of order greater than zero drop out: the result is

$$\begin{aligned} u_e(r, z) &= \frac{aE}{2} \sum_{\theta} \frac{1}{\theta^2 N_{n,\theta}} \left[\frac{f_0(a, \theta)}{\pi^2 k_e^2} - \frac{\phi_0(a, \theta)}{\pi^2 k_e k_i} \right] f_0(r, \theta) e^{-\theta z} & z < 0, \\ &= \frac{aE}{2} \sum_{\theta} \frac{1}{\theta^2 N_{n,\theta}} \left[\frac{f_0(a, \theta)}{\pi^2 k_e^2} - \frac{\phi_0(a, \theta)}{\pi^2 (k_e k_i)} \right] f_0(r, \theta) [1 - e^{-\theta z}] & z > 0. \end{aligned}$$

For sufficiently large values of z only the first term in the expansion need be kept; hence, to good approximation, ignoring, however, questions of convergence of the infinite series (cf. Jaeger, 1941)

$$u_e(r, z) = \text{const} \times f_0(r, \theta) e^{-\theta_0 z} \quad z < 0, \quad (18)$$

$$u_e(r, z) = \text{const} \times f_0(r, \theta) (1 - e^{-\theta_0 z}) \quad z > 0; \quad (19)$$

in like manner the interior potential is found to vary exponentially for large z ; consequently the membrane potential difference will also

be an exponential function of the distance from the injured region, the length constant being given by $1/\theta_0$.

An experimental study of the radial variation of the potential and current density around a passive iron wire conducting an impulse has been begun by Prof. F. L. Verwiebe and Mr. J. Lorenz.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

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FURTHER CONTRIBUTIONS TO THE MATHEMATICAL BIOPHYSICS OF VISUAL AESTHETICS

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

In previous papers cases were considered in which a visual pattern consists of a relatively small number of relatively strongly excited elements. Those cases are of interest in the theory of visual perception and aesthetic rating of artificial man made patterns. By an extension of the theory so as to take into account the finite thresholds of the inhibiting fibers a theory of aesthetic ratings of pattern consisting of a very large number of elements is outlined. This type of theory is applicable to natural patterns, such as landscapes.

In preceding publications (Rashevsky, 1938, 1940), we discussed the total central excitation resulting from the contemplation of some simple geometric pattern and by connecting that total excitation with the sensation of pleasure it was possible in some cases to predict theoretically the experimental rank order aesthetic ratings of some patterns. The excitation of each element of the pattern was considered as sufficiently strong, so that the thresholds of the inhibiting cross connecting fibers could be neglected. Under those conditions an optimum total excitation E is obtained for a definite number of elements. A pattern containing too many elements has a small E and therefore a small aesthetic rating, unless certain conditions of symmetry or of periodic repetition decrease the "effective" number of the elements.

Observation and experiment tend in general to confirm these conclusions, so far as geometric artificial or so to say "man made" patterns are concerned (Rashevsky, 1940). But when we consider the case of a beautiful scenery or a landscape painting, the simple theory is clearly inapplicable. For simple geometrical patterns we considered as elements such things as straight lines, angles, lengths, etc. Neurobiophysical structures were outlined which result in the perception of the above mentioned things as "elements". Similarly we can conceive of neurobiophysical mechanisms, which will correspond to the perception of a given color or shade as an "element" of the pattern. But a scenery or landscape painting consists of a tremendous number of such elements. The simple theory, applicable to elementary geometrical figures would predict complete mutual in-

hibition of such a large number of elements, which therefore could not be expected to have any aesthetic value at all.

Things are different however, if we consider the finite thresholds of the inhibitory fibers, leaving the rest of the neurobiophysical scheme unchanged. Equations for that case have been actually developed (Rashevsky, 1938, chap. xvii), in another connection.

Considering as before a set of n parallel excitatory neuronic chains corresponding to n peripheral stimuli or elements cross-connected by inhibiting chains and using the same notations as in *loc. cit.*, we find that if

$$h_1 < S_1 < h_1 + \frac{h_3}{P \alpha_1 I_1}, \quad (1)$$

(equation 56 of *loc. cit.*) then the inhibiting fibers remain unexcited and a central excitation results no matter how large the number n of elements of intensity S_1 . As a matter of fact the total central excitation increases under these conditions with increasing n .

If, however,

$$S_1 > h_1 + \frac{h_3}{P \alpha_1 I_1}, \quad (2)$$

(equation 59 of *loc. cit.*) then the inhibiting fibers come into play and this results in a complete central inhibition when

$$n > 1 + \frac{P}{Q} \frac{\alpha_1 I_1}{\alpha_3 I_3} \frac{S_1 - h_1}{P \alpha_1 I_1 (S_1 - h_1) - h_3}. \quad (3)$$

Only when $h_3 = 0$, inequality (2) is satisfied so soon as the first inequality (1) holds.

We may thus perceive a pattern consisting of a very large number of elements and derive an aesthetic satisfaction from it as long as the intensity of excitation of the different elements is not too great. The equations derived in *loc. cit.* hold for the case when all n elements are excited with equal intensity. But this can be readily generalized for different intensities of excitation, S_i , provided the S_i 's satisfy inequalities (1). Under these conditions a reduction of n results in a reduction of E and hence of the aesthetic value. On the other hand, keeping n constant but increasing some of the S_i sufficiently strongly, so as to satisfy inequality (3) may produce two effects. If the number of the strong S_i 's is small and the strength of these S_i 's is not too large, then although they will to some extent inhibit the remaining weaker elements, yet due to their own increased intensity of excitation, the total intensity E may even increase. If

however many S_i 's are strongly excited, this results in a complete inhibition.

The situation could be studied by using photographic pictures of the same landscape, showing different amount of details. Common experience tells us that an underexposed picture, lacking in details, is not so pleasant as a properly exposed one. An overexposed picture may both lack in details, as well as have too strong contrasts, and will not be pleasant either.

The difficulty for a quantitative experimental study lies not so much in the production of pictures with different number of elements as in the actual counting of these elements. The following suggestion may perhaps be used.

When a photograph of a landscape is scanned on a facsimile transmitter, the variations of shade are transformed into electrical impulses. By taking a continuous record of the current, which leaves the transmitter while the picture is being scanned, we shall obtain a line which has the more ripples or peaks, the greater number of elements the picture has. The number of individual ripples on the line of the recorded current may be used as a measure of the total number of elements on the picture. The record of the current produced by scanning a perfectly uniform sheet, with no elements, will give a horizontal line.

The same method could be used in principle for the production of pictures with different number of elements, starting with a "standard" picture. At the receiving end of a facsimile transmission outfit the current impulses are again transformed into photographic impressions of different shades of black and white. If, by suitable condensers or inductances¹ we distort the current curve in such a way that the smaller ripples on the curve disappear and feed such a distorted current into the receiver, we shall obtain a picture which has fewer elements. On the contrary, if by proper means, we distort the current curve in such a way, as not only to preserve all the ripples but to accentuate them, we shall have the case of increased S_i 's. The picture thus obtained will have the same number of elements as the "standard" picture, but they will be much more emphasized.

By such a method one could obtain a set of pictures with different numbers of elements, and a corresponding set of current-records, which will give us directly the number of elements. The aesthetic values of the pictures could then be determined by standard psycho-physical methods.

Individuals with very high h_1 and h_3 will enjoy much stronger

¹ This has been suggested to the Author by Mr. H. E. Stanton.

S_i 's, in other words much more pronounced contrasts in either shade or color. On the other hand individuals with very low h_3 will either prefer very simple patterns or like complex patterns with extremely vague contrasts. Thus we have a neurobiophysical interpretation of differences in tastes. Other neurological parameters also enter of course into the question as seen from equations (1), (2) and (3). Some peculiar characteristics of modernistic paintings with either rather "crying" colors or extreme "vagueness" may perhaps be interpreted in the above way in neurological terms.

Similar considerations may hold about sound patterns. High thresholds of inhibiting fibers would result in the preference of strong, harsh and sudden sound combinations.

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SOME OBSERVATIONS ON THE SIMPLE NEURON CIRCUIT

WALTER PITTS
THE UNIVERSITY OF CHICAGO

A new point of view in the theory of neuron networks is here adumbrated in its relation to the simple circuit: it is shown how these methods enable us to extend considerably and unify previous results for this case in a much simpler way.

I. Introduction and Definitions

The sequent remarks are intended primarily as a prolegomenon and an illustration of a more general theory of neuron networks to be later redacted. Herein, as in the more general discussion, we shall adopt the linear model of excitation as employed by A. S. Householder in four previous papers in this *Bulletin*; (Householder 1941a, b, c, 1942) our point of view will be somewhat different, however, in that we shall be primarily concerned with non-steady-state activity and the conditions under which a steady-state may be attained, rather than in the ascertainment of equilibrium points per se. We shall nevertheless find that this point of view has interesting consequences for problems of network statics.

We may commence by defining the *total conduction time* of a fiber as the sum of its conduction time and the synaptic delay at the postliminary synapse: we shall suppose, as can be done without substantive loss of generality, that all the total conduction times of fibers of the circuit C in question are equal: and we shall measure time so that this quantity is unity. We shall consider explicitly only the case where all fibers of C have remained unstimulated up to $t = 0$, a constant stimulation $\lambda_i + h_i$ is applied to each synapse s_i in the interval $t \in (0, 1)$, and the external stimulation assumes thereafter a steady value of s_i . We shall indicate desinently how all other cases are subsumable with inessential novations under this one.

We shall employ the same notation as in (Householder, 1941a, b, c, 1942) with ' A ' for the product of the activity parameters of C and the abbreviation $\mu_i = \sigma_i^{(n)}$, where there are n fibers in C . In addition to these, we shall find the following notations of value.

The excitation-pattern of C may be described in a *matrix* E , of n rows and an infinite number of columns, each of whose elements

e_{rs} represents the excitation at the synapse s_r during the interval $(s, s + 1)$. The successive entries in the excitation matrix E may be computed recursively from those in its first column—these are the quantities λ_r —by the following rule, whose validity is evident: Given the elements of the p -th column, compute those of the $p + 1$ -st thus: if the element e_{ip} is negative or zero, place σ_{i+1} in the $i + 1$ -st row and $p + 1$ -st column, or in the first row of the $p + 1$ -st column if $i = n$. Otherwise put $\sigma_{i+1} + a_i e_{ip}$ in this place. We shall say that C is in a *steady-state* during a series of n intervals $(s, s + 1), \dots, (s + n - 1, s + n)$ if, for every p between s and $s + n$, the p -th and $p + n$ -th columns of E are identical. If s is the smallest integer for which this is the case, we shall say that the steady state begins at the interval $(s, s + 1)$.

It will be seen that the construction of the matrix E implies that its infinite diagonals—where we take a diagonal to start again at the top of the succent column whenever it reaches the last row of E —are wholly independent of one another, so that if we know the starting point of a diagonal of E_s , we can calculate the entries along it uncognizant of any other values in the matrix. Physically, this of course means that the activity in C can be regarded as composed of wholly independent impulses, commencing originally at a synapse s_j with a value λ_j , and journeying around C in irrelation to the impulses beginning at other synapses. We shall find it convenient to adopt this standpoint, and consider only the case of a single impulse, so that the complete solution must be derived by combining the results of our subsequent procedures for the separate diagonals, and a steady-state for the whole circuit is attained only when one has accrued for each separate diagonal.

We may define a set of intervals for every synapse s_i , which we shall call the ranges of succeeding synapses s_{i+j} from s_i , and denote by $R_j(s_i)$, by the following recursion:

$$(1). \quad \text{If } a_i > 0, R_1(s_i) = (\sigma_{i+1}, \infty).$$

$$\text{If } a_i < 0, R_1(s_i) = (\sigma_{i+1}, -\infty).$$

$$(2). \quad \text{If } R_j(s_i) = (m, n), R_{j+1}(s_i) = (\sigma_{i+j+1} + ma_{j+i},$$

$\sigma_{i+j+1} + na_{j+i})$, unless m or n or both are negative, in which case we replace m or n respectively in this expression by 0.

If the range of s_{i+j} from s_i is (m, n) , the end-points m and n are denoted by $L_j(s_i)$ and $U_j(s_i)$. If $L_j(s_i) = U_j(s_i)$ for some j , s_j is said to be *inaccessible* from s_i ; otherwise *accessible*. Clearly, if the suffixes $i, j, h, 1$ are in cyclic order, $R_{k-i}(s_i)$ is a proper subset of the

range of s_k from s_j ; it is also inaccessible from s_i or any preceding synapse. Physically, that the range of s_j from s_i is (m, n) , where say $m < n$, means that by properly varying y_i , we can cause y_j to assume any value within the interval (m, n) ; but we cannot from s_i cause y_j to diminish beyond m , nor to exceed n . If s_j is inaccessible from s_i , then nothing happening at s_i will have any effect upon the excitation at s_j , and consequently, if a circuit contain any synapse inaccessible from anywhere, it will attain a steady state immediately, in the second n columns of E , and this steady state will be wholly independent of the initial stimulation λ_i . Incidentally, if at any time there are two zeroes between s_i and s_j , between which is an odd number of inhibitory fibers, s_j is inaccessible from s_i (cf. Householder 1941b, lemma 1).

We shall now find it desirable to establish two lemmas of importance, the first of which will be necessary for our more general theory, the second whereof is a special case of a result later to be established for general networks.

LEMMA 1

Let (m, n) be the range of a given synapse s_j from s_i . Suppose first that there are an even number of inhibitory fibers between s_i and s_j . Then we can find two numbers, ϑ_0 and ϑ_1 , $\vartheta_0 \leq \vartheta_1$, such that for all values of $y_i \leq \vartheta_0$ the consequent value of y_j is m ; for $\vartheta_0 < y_i \leq \vartheta_1$, the chain between s_i and s_j is completely active, and y_j is accordingly a linear function of y_i ; for $y_i > \vartheta_1$, $y_j = n$. Second, suppose there is an odd number of inhibitory fibers between s_i and s_j . Then we can choose ϑ_0 and ϑ_1 , $\vartheta_0 \leq \vartheta_1$, so that for $y_i \leq \vartheta_0$, $y_j = n$; for $\vartheta_0 \leq y_i < \vartheta_1$, y_j is a linear function of y_i , and there are no zeroes between s_i and s_j ; for $y_i > \vartheta_1$, $y_j = m$.

For convenience in statement, we shall assume an even number of inhibitory fibers between s_i and s_{i+j} ; the proof may be extended to the other case with inessential changes. It is clearly sufficient to show (1) that as we increase y_i from 0 to $+\infty$, then, unless $L_j(s_i) = -\infty$, when $\vartheta_0 = -\infty$, that intermediate zero between s_i and s_{i+j} which is nearest to s_{i+j} is removed at most once, to produce a state of complete activity; and (2), if we augment y_i still further, so that a new zero is formed—otherwise $U_j(s_i) = +\infty$, $\vartheta_1 = +\infty$ —this zero cannot be removed by further increase in y_i . (1) follows thus. At values of y_i sufficiently small so that if $R_j(s_i)$ is finite y_{i+j} is equal to it, there will be zeroes at synapses between s_i and s_{i+j} , of which one, say s_k is closest to s_{i+j} . Now suppose that, as we increase y_i , the zero at s_k is removed for a least value of y_i , say y_{i0} . Now if there were a zero between s_i and s_k , say at $s_{k'}$, which remained unchanged as y_i assumed

the value y_{i_0} , s_k could, of course, not be affected. If all zeroes between s_i and s_k disappeared for $y_i = y_{i_0}$, a state of complete activity would result, in accordance with (1). The only other possibility is that there be no zero between s_i and s_k for $y_i < y_{i_0}$, but one is initiated, say at $s_{k'}$, for $y_i = y_{i_0}$. Now if there is to be no interval of complete activity at all, then, precisely when the zero at $s_{k'}$ is formed, or $y_{k'} = 0$, and not at all before, s_k must cease to be a zero, so that $y_k > 0$. Now y_k is a linear function of $y_{k'}$ for all values of the latter greater than or equal to zero, since there is then no zero between them: consequently if, as is clearly possible, we select a small $y_{k'}$ satisfying $0 < y_{k'} < y_k$, $y_{k'}$ will be the value of this function for some argument $y'_{k'}$ which exceeds zero, by continuity and monotonicity; and since $y'_{k'} > 0$, the zero at s_k is broken down for this value of y_k also; and consequently for a $y'_{k'} > 0$, which is contrary to hypothesis. Hence (1) holds. (2) follows immediately: if we have complete activity between s_i and s_j for a given range of values of y_i , then all y_k for $i < k < j$ vary linearly with y_i ; and it is only when one of these, say y_k , diminishes (linearly) to zero that the complete activity is interrupted. Now if complete activity were to be reestablished for a higher value of y_i , then y_k , being the same monotone function of y_i , would be exceeded by zero, which is not compatible with complete activity. By (1), the zero formed at s_k could not be removed in any other way.

It is clear, by the continuity of the value of y_{i+j} as a function of y_i , that the quantities ϑ_{0i} , ϑ_i , and the ranges are connected by the important relations

$$L_j(s_i) = A_{i,i+j} \vartheta_0 + \sigma_{i+j}^{(j)},$$

$$U_j(s_i) = A_{i,i+j} \vartheta_1 + \sigma_{i+j}^{(j)}.$$

For the pair ϑ_0 , ϑ_1 in the case where $s_j = s_{i+n} = s_i$, as determined thus, we shall use the permanent notation ϑ_{0i} , ϑ_{1i} . In this case we have

$$L_n(s_i) = A \vartheta_{0i} + \mu_i,$$

$$U_n(s_i) = A \vartheta_{1i} + \mu_i.$$

LEMMA 2.

If a circuit C has been in complete activity for a period qn time-units in length, and $\xi < 1$, then the excitation of s_i at the time $qn + \xi$ is given by

$$y_i(qn + \xi) = \mu_i \frac{1 - A^q}{1 - A} + \lambda_i A^q, \quad (1)$$

and that at the synapse s_{i+j} , $j < n$, for any time $qn + j + \xi$, $\xi < 1$, by

$$y_{i+j}(qn + j + \xi) = \sigma_{i+j}^{(j)} + A_{i,i+j} \mu_i \frac{1 - A^q}{1 - A} + \lambda_i A^q. \quad (2)$$

If C is in complete activity we may write a difference equation for excitation at $t + n$ as a function of that at t ; this is

$$y_i(t + n) = \mu_i + A y_i(t).$$

One verifies that equation (1) is a solution of this by substitution; and equation (2) is an immediate consequence of equation (1).

Armed with these results, we shall easily be able to determine the possible types of activity in the circuit C . To this end we may divide the possible values of the activity y_i at s_i into three regions: first, the region Γ_1 , comprising those which are less than ϑ_{oi} , second the values $\vartheta_{oi} < y_i \leq \vartheta_{ii}$, making up Γ_2 , and third, the $y_i > \vartheta_{ii}$, which constitutes Γ_3 . Suppose the value of y_i at a given time belongs to Γ_1 , i.e., $y_i \leq \vartheta_{oi}$. By lemma 1, the consequent value of the impulse returning to s_i at $t + n$ will be $A \vartheta_{oi} + \mu_i$. If this is also less than ϑ_{oi} , the same value will recur at $t + 2n$; and we shall have a steady state of C determined by $y_i = A \vartheta_{oi} + \mu_i$; if, however, $A \vartheta_{oi} + \mu_i \geq \vartheta_{oi}$, the circuit will, by lemma 1, go into complete activity, and there will be no steady state with $y_i = A \vartheta_{oi} + \mu_i$.

Suppose that a given y_i belongs to Γ_2 , i.e., that $\vartheta_{oi} \leq y_i < \vartheta_{ii}$. Then C will be in complete activity, and, by lemma (2), the course of activity will be described by

$$y_i = \mu_i \frac{1 - A^t}{1 - A} + A^{t+1} \lambda_i.$$

Consider the value of this expression as t becomes very large. If $|A| > 1$, then, unless both μ_i and λ_i vanish, in which case also C is not in complete activity, y_i will increase indefinitely, so that a steady state with complete activity is not possible. If $A = \pm 1$, we arrive at a special case to be treated later. If $|A| < 1$, y_i will approach an asymptotic value

$$y_i = \frac{\mu_i}{1 - A},$$

and if this value for y_i puts C into complete activity, it will determine a possible steady state of complete activity: i.e., this will be the case

if and only if

$$\vartheta_{0i} \leq \frac{\mu_i}{1-A} < \vartheta_{1i}.$$

The possibility of a steady state for a y_i in Γ_3 may be treated analogously to that of Γ_1 : we shall have, as necessary and sufficient condition for the existence of such a value $y_i = A \vartheta_{1i} + \mu_i$ that $A \vartheta_{1i} + \mu_i \geq \vartheta_{0i}$. Collecting these conditions, we shall have the

THEOREM.

A circuit C may have at most three possible steady states:

A). *One given by $y_i = A \vartheta_{0i} + \mu_i$.*

B). *One given by $y_i = \frac{\mu_i}{1-A}$*

C). *One given by $y_i = A \vartheta_{1i} + \mu_i$.*

Necessary and sufficient conditions for the actual existence of each of these are given respectively by the requirements:

A). $\mu_i \leq (1-A)\vartheta_{0i}.$

B). $\vartheta_{0i} < \frac{\mu_i}{1-A} \leq \vartheta_{1i}, \quad |A| < 1.$

C). $\mu_i > (1-A)\vartheta_{1i}.$

By way of corollary from these conditions—which differ from those of (Householder, 1941b and c) in giving explicit expressions for the equilibrium points—we may derive the general results of (Householder, 1941b and c) for the simple circuit in a very much easier way. Suppose first that $0 < A < 1$. Then (A), (B), and (C) become

A'). $\frac{\mu_i}{1-A} \leq \vartheta_{0i}.$

B'). $\vartheta_{0i} < \frac{\mu_i}{1-A} \leq \vartheta_{1i}, \quad |A| < 1.$

C'). $\frac{\mu_i}{1-A} < \vartheta_{1i}.$

Clearly one, and only one of these conditions can be fulfilled by a given circuit. We shall consequently have the

COROLLARY.

When $0 < A < 1$, the circuit C has a unique steady-state activity

pattern. This will also be the case when $A < -1$, except that here no steady state of complete activity is possible.

Suppose now that $A > 1$. Here again, condition (B) is excluded, and there is no steady state of complete activity; the other possibilities may be expressed as

$$A''). \quad \frac{\mu_i}{1-A} > \vartheta_{0i}$$

$$C''). \quad \frac{\mu_i}{1-A} \leq \vartheta_{1i},$$

which are not incompatible, so that we may well have two possible steady states, given by $A\vartheta_{0i} + \mu_i$ and $A\vartheta_{1i} + \mu_i$ respectively, both of which contain at least one zero.

It may be desired to trace the course of activity in C from the initial value λ_i to whatever steady state, if any, is finally reached. This may be done without difficulty by considering which region contains λ_i , the initial value of y_i . If this region contain a possible steady-state value of y_i , then, if it is Γ_1 or Γ_3 the steady state will obviously be attained immediately, while if it is Γ_2 , it will be approached asymptotically, in accordance with (1). If the region containing λ_i do not contain a steady state then, if it be Γ_1 or Γ_3 the value of y_i will enter immediately and move through the adjacent regions until the first one containing a steady state is entered, whereupon that steady state is either attained immediately or asymptotically accordingly as this final region is Γ_1 or Γ_3 , or is Γ_2 ; while if the initial region of y_i be Γ_2 then, if only one of Γ_1 , Γ_2 contain a possible steady state value, then that one will be entered, at a time determinable by solving (1) for t with $y_i = \vartheta_{0i}$ or ϑ_{1i} accordingly as the final region be Γ_1 or Γ_3 ; but if both Γ_1 and Γ_3 contain possible steady states, y_i will be described by (1) until that value $y_i = \vartheta_{0i}$ or ϑ_{1i} which occurs first befalls, whereupon it goes into the steady state of Γ_1 or Γ_3 respectively.

It will be worth while to conclude our discussion with a consideration of the interesting and important case where $A = \pm 1$. We notice first that if $A = \pm 1$, then the conditions (A) and (C) of the theorem become

$$A'''). \quad \mu_i \leq 0$$

$$C'''). \quad \mu_i \geq 0,$$

at least one of which must hold, so that there always exists a steady state for C with at least one zero in this case. The interesting case

arises when we have complete activity, however, at least initially, so that we shall suppose $\vartheta_{0i} < \lambda_i \leq \vartheta_{1i}$. Equation (1) becomes in this case

$$y_i = \mu_i \frac{1 - (\pm 1)^t}{1 - (\pm 1)} + (\pm 1)^{t+1} \lambda_i,$$

for the values of t specified in lemma 2, which is indeterminate; evaluating the quotient by limits we obtain

$$y_i = t \mu_i (\pm 1)^t + (\pm 1)^{t+1} \lambda_i. \quad (3)$$

If $\mu_i \neq 0$, y_i becomes indefinitely large with t , so that a steady state of complete activity is not possible; and the case has no special interest. When $\mu_i = 0$, however, we have

$$y_i = (+1)^{t+1} \lambda_i. \quad (4)$$

In the case $\lambda_i = +1$, this means that the circuit C has an *infinitude of possible steady states*, one for each value of λ_i satisfying $\vartheta_0 \leq \lambda_i < \vartheta_{1i}$, so that the parameters of C do not determine the steady state conditions even among a finite set of values. Another such case arises when $\lambda_i = -1$; here, however, we have no steady state at all, but instead continual oscillations in C of amplitude $|\lambda_i|$. It may be remarked that this possibility might have been determined by the methods of (Householder, 1941a, b, c) except for an oversight: the application of Cramér's rule on page 68 of (Householder, 1941a) is invalid when $A = 0$, which is equivalent to supposing $A = 1(\Delta = 1 - A)$; on account of this the principal result of (3) is not in general valid. If the \leq sign be struck out of the statements of this result, however, and replaced by $<$, it becomes correct. A similar correction can generally be made at a few other places in (Householder, 1941a, b, c, 1942) where this oversight enters. The two possible cases in respect of the equations (7) of (Householder, 1941a), namely inconsistency and indeterminacy, correspond respectively to the case where μ_i does and does not vanish for all i . In the first case, as we saw above, equation (2) gives an indefinitely great y_i for sufficiently late t , and no steady state of complete activity is indeed possible; in the second we have the determination of the substantial one of an infinite number of possible steady states by the initial values λ_i , as we should infer from the equations (7) of (Householder, 1941a) in this case.

We may perhaps conclude the present discussion with two remarks. First, with regard to the relationship of our present analysis to the purely static one of (Householder, 1941a, b, and c); we have been able to obtain all the results there found with a rather simpler procedure. We are, moreover, enabled to solve explicitly a problem

treated less directly in (Householder, 1941a, b, and c). A theorem there enables us to calculate all the stimulus patterns consistent with one or two specified activity patterns; since there are only a finite number of activity patterns, we can always enumerate them until we find all the pairs consistent with any given stimulus pattern, which is what we really want. This method may be very laborious, however: there are 2^n distinct *AP*'s, and $2^n \cdot (2^n - 1)$ pairs to be tested in general. Theorem 1 above on the contrary enables us to determine at once explicitly how many steady states there are in any given circuit, and what values of y_i determine them.

Secondly, the above results may be extended (1) to the case where the initial stimulation between $t = 0$ and $t = 1$ is not a constant λ_i , but a bounded function $y_i(t)$, by simply dividing the interval $(0, 1)$ into sufficiently small segments so that all points of a given segment, when taken as the λ_i above, permit the circuit to approach the same steady state in the same way; the predictions thus obtained for each segment are to be applied only throughout those later time-intervals which are congruent to it modulo n ; (2), to cases where the initial variation in stimulation has lasted arbitrarily long before becoming steady, by waiting until the last synapse of C receives a steady stimulation, counting that interval as the first, and applying (1).

Desinently, I should like to express my appreciation of the counsel and criticisms of Dr. A. S. Householder, who suggested the problem of this and later papers on the theory of neuron networks.

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DELAYED ADSORPTION AND DIFFUSION IN COLLOIDAL MEDIA

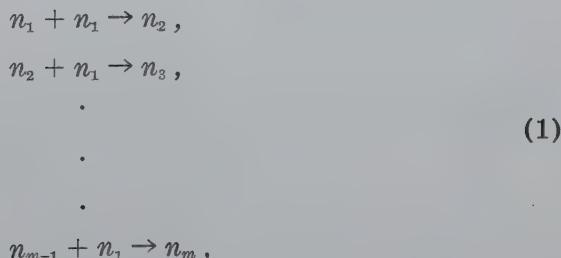
HERMAN BRANSON

HOWARD UNIVERSITY, WASHINGTON, D. C.

The behavior of the diffusion coefficient of a solute which can be adsorbed by a colloid only after the colloid has aggregated to a certain size is deduced on the basis of a few assumptions. Some relations of such a mechanism to cell reactions are indicated.

A type of reaction plausible in cell behavior is one in which two or more substances may be released under a stimulus. This paper considers such a release with two substances one of which can aggregate into larger micelles and upon reaching an optimum size adsorbs the second substance, which we call the solute. After this initial adsorption we may consider either no further aggregation and adsorption or further aggregation with adsorption as being the possibilities of greatest interest. For our purposes the significant point is what effect these alternative possibilities have upon the diffusion coefficient of the solute. In addition, we indicate how this mechanism may be used to interpret certain reactions in a cell, e.g. reactions which begin at a certain rate, proceed at that rate for some time, and then fall to a minimum.

The aggregation of the colloid particles is assumed to take place in the following chain:



where n_m is the size at which adsorption of the solute occurs. This chain expresses the assumption that a higher aggregate is formed from the next lower by the adjoining of a simple micelle, in short there is no aggregation of higher aggregates with each other. We

shall consider first the mechanism which allows no aggregation after adsorption. The differential equations for this chain are

$$\begin{aligned}\frac{dn_1}{dt} &= -k_1 n_1^2 - k_2 n_1 n_2 - \dots - k_{m-1} n_1 n_{m-1}, \\ \frac{dn_2}{dt} &= \frac{k_1 n_1^2}{2} - k_2 n_1 n_2, \\ &\vdots \\ &\vdots \\ \frac{dn_e}{dt} &= k_{e-1} n_1 n_{e-1} - k_e n_1 n_e, \\ &\vdots \\ &\vdots \\ \frac{dn_m}{dt} &= k_{m-1} n_1 n_{m-1}.\end{aligned}\tag{2}$$

On making the substitution $n_i d t = d x$ these equations are transformed into the linear forms

$$\begin{aligned}\frac{dn_1}{dx} &= -\sum_{i=1}^{m-1} k_i n_i, \\ \frac{dn_2}{dx} &= \frac{k_1}{2} n_1 - k_2 n_2, \\ &\vdots \\ \frac{dn_r}{dx} &= k_{m-1} n_{m-1}.\end{aligned}\tag{3}$$

The characteristic equation of this set is

$$\left| \begin{array}{cccccc} \lambda + k_1 & k_2 & k_3 & \dots & k_{m-1} & 0 \\ -\frac{k_1}{2} & \lambda + k_2 & 0 & \dots & \dots & 0 \\ 0 & -k_2 & \lambda + k_3 & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots & -k_{m-1} & \lambda \end{array} \right| = 0. \tag{4}$$

A simple relationship is found between the determinants of each or-

der. Consider for $m = 3$ we have

$$D_2(\lambda) = \begin{vmatrix} \lambda + k_1 & k_2 \\ -\frac{k_1}{2} & \lambda + k_2 \end{vmatrix},$$

observe that

$$D_3(\lambda) = (\lambda + k_3) D_2(\lambda) + \frac{k_1 k_2 k_3}{2},$$

and in general

$$D_e(\lambda) = (\lambda + k_e) D_{e-1}(\lambda) + \frac{k_1 k_2 \dots k_e}{2}. \quad (5)$$

Inasmuch as we shall not treat the general case, except to observe that the physical conclusions will probably not be much different for large values of m , we can state that in order to be physically meaningful the solutions of equation (3)

$$n_k = \sum_{j=1}^m c_{kj} e^{\lambda_j x} \quad (6)$$

satisfy the boundary conditions at all values of time

$$\sum_1^m k n_k = n_0.$$

Since x and not time occurs in equation (6), we see that it is not necessary that the real part of the λ be negative. From the defining equation for x , we have $x \rightarrow x_0$, x_0 finite, $n_1 \rightarrow 0$, then $t(x) \rightarrow \infty$; thus an infinite time is required for all the n_1 to disappear even though the x_0 is finite.

All the information needed for our purpose can be had from a detailed treatment of the set for $m = 3$. That is there will be an aggregate of three colloid particles built up before adsorption of the solute occurs. The problem immediately suggested is the relative behavior of n_1 and n_2 . This behavior can be obtained from the integral curves. Using the notation of L. R. Ford (1933),

$$\frac{dn_2}{dn_1} = \frac{-\frac{k_1}{2} n_1 + k_2 n_2}{k_1 n_1 + k_2 n_2}, \quad (7)$$

$$\Delta = (k_1 + k_2)^2 - 6 k_1 k_2.$$

Since $k_1 + k_2 \neq 0$, the integral curves are not conics.

For

$$M_1: \quad n_2 = \mu_1 n_1 \quad M_2: \quad n_2 = \mu^2 n_1$$

where

$$\mu_{1,2} = \frac{-(k_1 - k_2) \pm \sqrt{\Delta}}{2 k_2}, \quad (8)$$

the integral curves are shown in Figure 1.

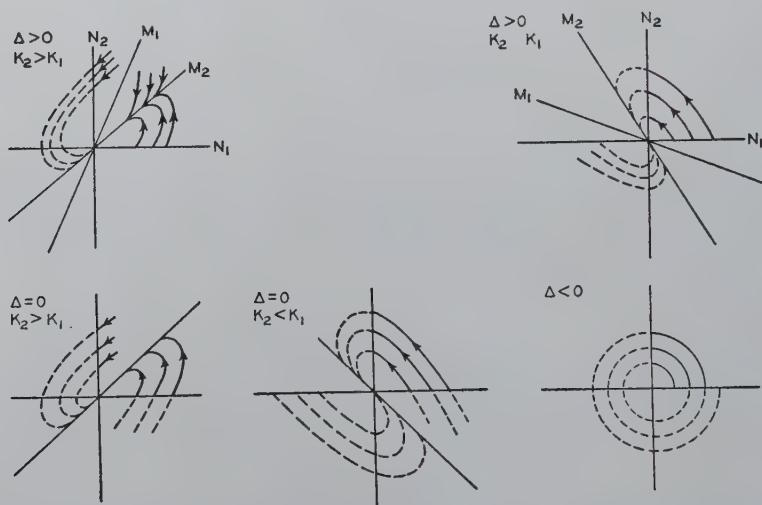


FIGURE 1

These solutions are physically well-behaved in that all show that either n_1 disappears before n_2 or they disappear together. But the presence of n_2 after the disappearance of n_1 , makes it impossible for all of n_2 to be transformed into n_3 . Thus for the simple case of n_1 , n_2 , n_3 , we can expect as a resultant state only n_3 or a mixture of n_2 and n_3 . The first will result if $k_2 > k_1$ and $\Delta \geq 0$. The k 's will be determined by the reaction, hence in a specific experiment we can examine the products present after sufficient time which will decide whether n_2 and n_3 or only n_3 remains.

An alternative treatment of the integral curves which is immediately applicable to the general case has been suggested in a letter by Dr. A. S. Householder. From the conditions, the integral curves in the n_2 , n_1 plane are confined to the region bounded by the coordinate axes and the line $n_1 + 2n_2 = n_0$. Since $dn_1/dx < 0$ for any n_1 and n_2 not both zero, the integral curve can cross the n_2 axis ($n_1 = 0$). While for $n_2 = 0$, unless $n_1 = 0$ simultaneously, the integral curve is directed into the region. The scalar product of the vector with the

normal is $-3k_2 n_2$ which is always negative for $n_2 > 0$. Initially $n_2 = 0$ and $n_1 = n_0$, thus the curve begins at the intersection of the line $n_1 + 2n_2 = n_0$ and the n_1 axis; the integral curve is tangent to the line and directed upward from the n_1 axis. As n_2 builds up the integral curve turns inward away from the line $n_1 + 2n_2 = n_0$.

The general set is treated in the same manner. Here the integral curves are confined to the region bounded by the $m-1$ coordinate hyper-planes and the hyper-plane $\sum_1^{m-1} k_n n_k = n_0$. The integral curve can cross the hyper-plane $n_1 = 0$ for always $dn_1/dx < 0$. But when $n_k = 0$, $k \neq 1$, $dn_k/dx = k_{k-1} n_{k-1} > 0$ unless n_{k-1} is also 0; but if n_{k-1} is 0, $dn_{k-1}/dx > 0$, etc., until we meet an $n_r \neq 0$. Hence if any n_k , $k \neq 1$, approaches zero the integral curve turns toward a region where the n_k is increasing. Finally the scalar product of the tangent and the outward normal is $-(m-1) k_{m-1} n_{m-1}$ which completes the proof that for a finite x , but an infinite t , n_1 vanishes in the general case; and although some of the other n 's may vanish simultaneously with n_1 , they cannot vanish ahead of n_1 .

The solutions of the set satisfying the boundary conditions

$$n_1 + 2n_2 + 3n_3 = n_0,$$

and at $x = 0$, $n_1 = n_0$ where n_0 is the initial number of simple colloid particles, are

$$\begin{aligned} n_1 &= \frac{n_0}{\lambda_1 - \lambda_2} \left[(\lambda_1 + k_1) e^{\lambda_1 x} - (\lambda_2 + k_1) e^{\lambda_2 x} \right], \\ n_2 &= \frac{n_0 (\lambda_1 + k_1) (\lambda_2 + k_1)}{k_2 (\lambda_1 - \lambda_2)} \left[e^{\lambda_1 x} - e^{\lambda_2 x} \right], \\ n_3 &= \frac{n_0}{3} \left[1 + \frac{3(\lambda_1 + k_1)(\lambda_2 + k_1)}{\lambda_1(\lambda_1 - \lambda_2)} e^{\lambda_1 x} \right. \\ &\quad \left. - \frac{3(\lambda_1 + k_1)(\lambda_2 + k_1)}{\lambda_2(\lambda_1 - \lambda_2)} e^{\lambda_2 x} \right], \end{aligned} \tag{9}$$

where

$$\lambda_{1,2} = \frac{-(k_1 + k_2) \pm \sqrt{A}}{2}.$$

The relation between x and t is $n_1 d t = d x$

$$t = \int_0^x \frac{dx}{n_1}$$

where $x = 0$ when $t = 0$. Before the integration can be performed the upper limit must be fixed. Calling this upper limit x and recalling that we are concerned about the value of the time from the beginning of the reaction until the appearance of the first particle capable of adsorbing a solute particle, we have on introducing $n_3 = 1$ into (9) and calling the coefficients of exponentials α and β respectively

$$3/n_0 = 1 + \alpha e^{\lambda_1 x} - \beta e^{\lambda_2 x}. \quad (10)$$

This equation cannot be solved explicitly for x . Making the substitutions

$$y_1 = \alpha e^{\lambda_1 x} + 1 - 3/n_0,$$

$$y_2 = \beta e^{\lambda_2 x},$$

we can solve graphically if we have numerical values for α , β , and n_0 . Taking $n_0 = 1000$, $k_2 = 4$ $k_1 = 4$ k then $\Delta = k^2$, $\lambda_1 = -4k$, $\lambda_2 = -6k$ and we find $\alpha = -5.55$, $\beta = 3.75$. Substituting these values we have $x = 0.48/k$.

$$\tau = \frac{2}{1000} \int_0^x \frac{e^{4kx}}{5 - 3 e^{-2kx}} d x,$$

where τ is the time required for the first n_3 to appear in the system. Integrating numerically by using Simpson's rule, we find

$$\tau = 48.18/1000 k \text{ secs.} \quad (11)$$

Our analysis culminating in (11) can be summarized: when the aggregation takes place according to (3) with $m = 3$, at the end of $48.18/1000 k$ secs. the particles capable of adsorbing solute particles appear in the system. Before their appearance, the other colloid particles would have negligible effect upon the diffusion coefficient of the solute. After their appearance, however, they would act to reduce the value of D according to J. Reiner's curve (1939). The effect is shown in Figure 2a. If the aggregation continues with the number of adsorbed solute particles a function of the surface area as in an

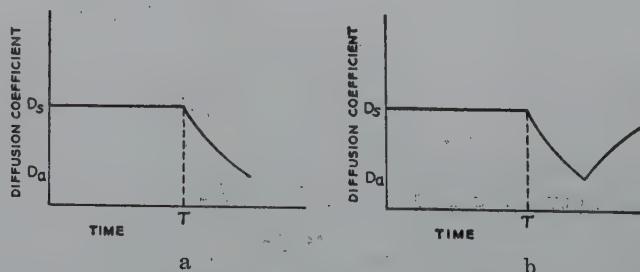


FIGURE 2

earlier paper (H. Branson, 1942), we would have the variation represented in Figure 2b.

In order for the mechanism to be applicable to cellular reactions, τ has to be in general small, except for some reactions where it may be of the order of a second. From physical considerations we see that k is a function of the diffusion coefficient and the radius of the aggregating particles; M. V. Smoluchowski (1918) found for a colloid solution $k = 4 \pi \tau D$. Introducing values given in that paper from Zsigmondy's experiments we have $k \approx 10^{-12}$ and $\tau \approx 10^{10}$ secs. Thus unless the diffusion coefficient within the cell is considerably larger than in solution, this reaction gives an inordinately long time for the beginning of the decrease in the diffusion coefficient. More plausible values of τ can be obtained by considering n_o to be much larger in (10). Raising n_o to 10^7 causes practically no change in x , and taking $r \approx 10^{-6}$ cm then for D of the order of 10^3 , τ will be of the order of a hundredth of a second. This is not an unreasonable value of D for aggregations where the binding energy is large.

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AN EXPRESSION FOR THE RATE OF RETURN OF AN EGG AFTER ARTIFICIAL DEFORMATION

H. D. LANDAHL
THE UNIVERSITY OF CHICAGO

The forces which may be involved in the restoration of a deformed cell to its normal shape are considered. Estimates of the order of magnitude of the forces suggest that the most important forces are those due to surface tension, membrane elasticity and viscosity. An approximate expression is then derived for the rate of return of an elongated or compressed egg. The former expression is compared with data on eggs of *Arbacia* by E. N. Harvey and H. Shapiro, and it is found to agree sufficiently well with the data. The initial surface force is too low compared with that given by K. S. Cole but various factors are discussed which could contribute to this discrepancy. The value for the net viscosity of the egg is about twice the value arrived at by L. V. Heilbrunn for the egg protoplasm.

If a cell is deformed by an external force, various forces may tend to restore it to the normal shape. These may be grouped into surface forces and volume forces. The surface forces may be subdivided into surface tension, elastic membrane tension and osmotic forces. The former is independent of area, while the second is probably directly proportional to the change in area, at least over the initial range. The volume forces may be due to electrical or diffusion phenomena. The effect of electrical forces can probably be neglected (Rashevsky, 1938, Williamson, 1939). The same may be true for electrical surface forces. If the period for return to normal after deformation is short compared with the time constant, Λ , of diffusion processes (Landahl, 1939), we may consider the diffusion field as constant. For *Arbacia* eggs, Λ for oxygen is about four seconds, and that for other metabolites probably considerably greater. Then the effect of diffusion and osmotic forces will have little effect on the form of the curve of change of shape. As the eggs do not appreciably deform under the action of gravity, we shall neglect this volume force. Thus none of the volume forces will be considered.

Opposing the surface forces are those due to the inertia and the viscosity of the material of the egg itself, the latter being the resultant of the viscosity of the protoplasm including the effect of the granules, internal structure, and membrane, as well as the viscosity of the surrounding medium. The effect of this latter viscosity is roughly

to add to the net effect of the cell viscosity. This may be seen in the expression obtained by J. A. Wheeler for the "relaxation" time in the case of a true surface tension (Harvey and Shapiro, 1941). Since the effect of the cell is then at least several times that of the surrounding medium, the assumption of simple additivity introduces a negligible error. The inertial terms are not more than a fraction of a per cent of the term due to surface forces. They may be estimated as follows. At any instant the force due to inertia will not be of a greater order of magnitude than if the half mass were accelerated at the rate at which the pole is accelerated. This product of the half mass with the acceleration gives a force which may be compared with the effect of surface tension for that particular degree of elongation. An estimation indicates that the former is at most a fraction of a per cent of the latter. An assumption of an elastic membrane force only increases the effect at greater elongations and it is only for these shapes that the inertial effect is at all appreciable. Hence we shall not consider the effect of inertial terms.

Let $2r_1$ be the length and $2r_2$ the width of a deformed cell whose diameter in the spherical shape is $2r_o$. We shall assume that any deformations can be approximated by an ellipsoid of revolution about the z -axis, along which r_1 is measured. Let the surface force per cm. at any point be $\gamma'(x, y, z) = \gamma'(\rho, z)$, where $\rho^2 = x^2 + y^2$. If K_1 and K_2 are the principle curvatures at (ρ, z) and γ'_1 and γ'_2 are surface forces per cm. in the respective directions, then the normal component is $\gamma'_1 K_1 + \gamma'_2 K_2$. The component of γ' which is due to a surface tension is independent of deformation, and can be treated without too great difficulty. The component due to an elastic membrane tension is of a different order of complexity. For this reason, in order to treat the problem, we shall introduce an approximation and for the present only consider the deductions which then follow. We shall assume that the elasticity is the same in any direction, though, in general, it may not be isotropic. We shall introduce an average surface force γ which is the average value of $\gamma_1 + \gamma_2$ over the surface for a particular deformation. We shall further assume that γ varies approximately linearly with increase in area, or that

$$\gamma = \gamma_0 + \frac{\zeta \Delta S}{S_0}, \quad (1)$$

where S_0 should be taken as the surface of the sphere of no membrane tension, ΔS is the change in the surface and ζ is a constant. Without much error one can let $S_0 = 4 \pi r_o^2$ and measure the area changes from this value. That the relation of (1) is then approximately lin-

ear in the case of *Arbacia* eggs is indicated by unpublished data furnished by Dr. K. S. Cole. The value of ζ is in this case about 0.58 dynes per cm. If one takes the value for the membrane tension .19 dynes per cm. given by Harvey (1931) for a twenty-five per cent increase in surface area and uses the value .08 for the initial value (Cole, 1932) one obtains $\zeta = 0.44$ dynes per cm., a value which agrees rather well with that above.

It may be pointed out in this connection that the surface force measured by Cole (1932) by the compression method is a quantity of the same type of average as γ used here. Evidently when the shape is only infinitesimally different from a sphere the error in γ is negligible. But for large deformations the error introduced may become considerable.

The relative rate of change of the half length, r_1 , under the influence of surface forces only, is given by Betti's theorem applied to plastic flow by the equation

$$\frac{1}{r_1} \frac{dr_1}{dt} = \frac{1}{3\eta V} \iint [zZ - \frac{1}{2}(xX + yY)] dS, \quad (2)$$

where V is the volume of the cell, η is the viscosity, X , Y and Z are the components of the surface forces along the x , y and z axes. The integration has been carried out by G. Young (1939) for the case in which the cell is a prolate ellipsoid of revolution. The result is [Young, 1939, equation (72)]

$$\frac{1}{r_1} \frac{dr_1}{dt} = -.53\beta \frac{\gamma}{\eta} \frac{(r_1 - r_2)}{r_1 r_2}, \quad (3)$$

where $\beta = 1$ for $r_1 = r_2$, $\beta = .94$ for $r_1 = 2r_2$ and $\beta = .74$ for $r_1 > > r_2$. We shall be interested in a range $r_1 = r_2$ to $r_1 \approx 2r_2$ so that we may set $\beta = 1$ without appreciable error. A consideration of the case of the oblate ellipsoid shows that equation (3) again holds, but β takes on slightly different values. Considering constant volume so that

$$r_1 r_2^2 = r_0^3, \quad (4)$$

and setting

$$\varepsilon = \frac{r_1 - r_0}{r_0}, \quad (5)$$

we may write equation (3) in the form

$$\frac{d\varepsilon}{dt} = \frac{-53\gamma}{\eta r_0} [(1 + \varepsilon)^{3/2} - 1]. \quad (6)$$

In order to integrate equation (6), it is first necessary to obtain the relation between γ and ε . This follows directly when we find the relation between $\Delta S/S_0$ and ε . Substituting the value of the area of a prolate ellipsoid of revolution into $(S - S_0)/S_0$ and using equations (4) and (5) we have an expression for $\Delta S/S_0$ in terms of ε . Evaluating the square root of $\Delta S/S_0$ numerically for values of ε and plotting the result one finds an approximately straight line relationship in the range $\varepsilon = 0$ to $\varepsilon = 0.6$. Deviation becomes marked beyond this, the function being concave downwards. For the oblate ellipsoid, the curve becomes markedly concave upwards beyond about $\varepsilon = -0.4$. In the range of ε from -0.3 to 0.6 we may write

$$\frac{\Delta S}{S_0} = 0.4 \varepsilon^2 (1 - 0.8\varepsilon + \dots), \quad (7)$$

where the error is about twenty per cent at the extremes. The range in $d\varepsilon/dt$ which we wish to consider is found experimentally to vary by a factor of the order of a hundred in the range of from 0.1 to 0.6 . Thus a considerable error in $d\varepsilon/dt$ at any point can be tolerated.

Introducing equation (7) into (1) and the resulting equation into (6) we obtain,

$$\frac{d\varepsilon}{dt} = -\frac{.80}{\eta r_0} (\gamma_0 + 0.4 \zeta \varepsilon^2) \varepsilon, \quad (8)$$

where we neglect the factor $(1 + \varepsilon/4 - \varepsilon^2/24 + \dots)$ from the expansion of the brackets in equation (6), as well as the factor $(1 - 0.8\varepsilon + \dots)$ of equation (7). The error in neglecting the first factor is not more than fifteen per cent, while that of the second factor may be about fifty per cent at $\varepsilon = 0.7$, but in the opposite direction. It is equivalent to requiring that 0.4ζ is larger than $\gamma_0(6/\varepsilon - 1)/24$. Since we shall not consider values of ε less than about 0.05 , this amounts to requiring that γ_0 should be less than about 0.05 .

Integrating equation (8) and setting $\varepsilon = \varepsilon_0$ for $t = 0$, we obtain

$$t = \frac{.63 \eta r_0}{\gamma_0} \log \frac{\varepsilon_0^2 (\gamma_0 + .4 \zeta \varepsilon_0^2)}{\varepsilon^2 (\gamma_0 + .4 \zeta \varepsilon_0^2)}. \quad (9)$$

The above expression might be expected to apply approximately for the recovery of a cell which had been compressed between two parallel planes and then released, as well as to the case in which a cell was elongated as a figure of revolution and then released. The necessity to assume an averaged γ in the integration presents itself as a difficulty. The error involved may not in general be the same for the prolate and oblate ellipsoids. Thus, to that extent, agreement be-

tween corresponding parameters obtained from the two procedures would tend to justify the approximate treatment used. One would allow a slight overestimation of perhaps twenty per cent in one case and a corresponding underestimation in the other due to the fact that the errors in equation (8) are in the opposite direction.

It may at times be convenient to use the ratio of the length to the width as a measure. If this is designated by R , one may substitute for ε the value $\varepsilon = R^{2/3} - 1$ in equation (9) and obtain an expression for the ratio of length to width as a function of time.

We shall now compare the relationship described by equation (9) with the experimental results obtained by E. N. Harvey and H. Shapiro (1941) from *Arbacia* eggs returning to normal after having been passed through sufficiently small capillaries to elongate them. From the length of the cell, r_1 , at any instant, the value of ε can be obtained by equation (5), so that an empirical $\varepsilon(t)$ relation is obtained. Comparing equation (9) with this relationship, one can determine the parameters. The $\varepsilon(t)$ relation is thus determined, and because of equation (4) and the condition for constant volume, $r_1(t)$ and $r_2(t)$ are determined.

In comparing equation (9) with the empirical relation, it is found that the value of γ_0 is required to be less than about 0.01, (and greater than about -0.002) or the empirical relation does not even approximately agree with the theoretical. Within this range the ratio of the parameters η/γ_0 to ζ/γ_0 is nearly constant and approximately the same as that obtained when γ_0 is taken equal to zero, for which $\eta/\zeta = 0.36 \text{ cm. sec.}^{-1}$. Hence, we shall use $\varepsilon(t)$ as if $\gamma_0 = 0$, though only requiring that it should not be larger than about 0.01. This restriction is sufficient to satisfy the previous condition that γ be less than 0.05. Instead of equation (9) we then obtain the equation

$$\varepsilon = \sqrt{\frac{\eta r_0 \varepsilon_0^2}{\eta r_0 + .64 \zeta \varepsilon_0^2 t}}. \quad (10)$$

Introducing this expression for ε into (4) and (5) we obtain $r_1(t)$ and $r_2(t)$. Since it is the length, $2r_1$, and width $2r_2$, which are measured, we write

$$2r_1 = 2r_0 [1 + \{\varepsilon_0^2 / (1 + .64 \zeta \varepsilon_0^2 t / \eta r_0)\}]^{\frac{1}{2}}, \quad (11)$$

$$2r_2 = 2r_0 [1 + \{\varepsilon_0^2 / (1 + .64 \zeta \varepsilon_0^2 t / \eta r_0)\}]^{-\frac{1}{2}}. \quad (12)$$

When $\eta/\zeta = 0.36$, $\varepsilon_0 = 0.72$ and $2r_0 = 76 \times 10^{-4} \text{ cm.}$, we obtain the curves shown in Figure 1. Using the value $\zeta = 0.58$ given above, we then obtain $\eta = 0.21$ poise. To obtain the net viscosity of the egg,

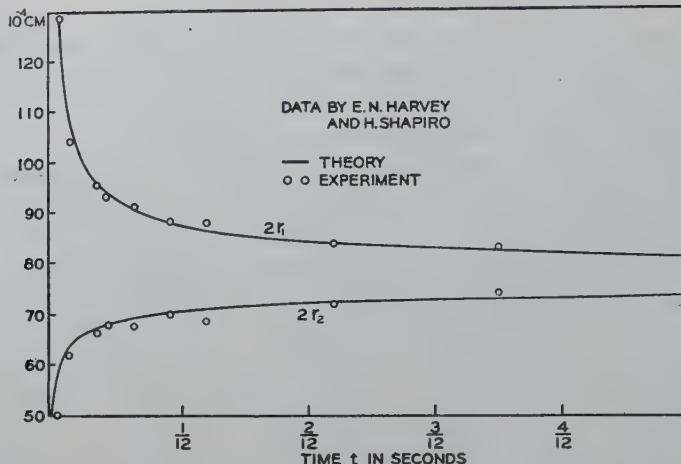


FIGURE 1

one should subtract approximately .01 because of the surrounding medium and perhaps allow for overestimation as mentioned above, giving $\eta_e = 0.16$ poise. The value η_e should be the total effective viscosity of the egg as a whole, if one could rely upon the approximations made. According to Heilbrunn, (1928), the viscosity of the fluid portion of the *Arbacia* egg is about .03 poise, while the viscosity uncorrected for granules is about 0.07 poise. The presence of larger structures may contribute appreciably to the total effective viscosity. Just to what extent this may be, would require a more detailed analysis. There is also the possible effect of the various membrane layers which affect the net viscosity. If we could assume that the value of $\eta_e = 0.16$ is correct, then we should conclude that the contribution to η_e by structures and membranes would be an amount approximately equal to that due to the protoplasm with granules. This would not imply that the amount contributed by the membrane gives its viscosity, though it may be possible to estimate it. In any case the value of η_e obtained is sufficiently plausible as to the order of magnitude. Using the value of ζ from the data by E. N. Harvey given above, we obtain $\eta_e = 0.11$ poise.

If the external viscosity instead of being that of water were increased by a factor of 15, the above estimates would predict that the constant of the curve, η/ζ , would be about doubled. Conversely one could thus determine the effective viscosity of the egg approximately as that value of the external viscosity which just doubles the constant η/ζ .

Thus far we have only required that γ_o be of the order or less

than about 0.01 dynes per cm. The value for summer eggs, as measured by K. S. Cole (1932), is 0.08 dynes per cm. Only one-half this value is obtained for late summer eggs (Cole and Michaelis, 1932). In the experiments under discussion, late season eggs were used. This is still probably too large a discrepancy to overlook, so we seek some explanation. Until the more exact solution to the problem, as mentioned above, is given, one cannot exclude the possibility that there would be no disagreement if the complete solution were known.

Since equations (11) and (12) represent the data, we can say that the rate of change of ε is approximately proportional to ε^3 . If a true surface tension is assumed, we see from equation (6) that the rate is approximately proportional to ε . The approximation made initially, of an average effective γ , probably has the effect of increasing the restoring force for large elongations. Also as the shapes diverge from the elliptical shape in the direction of a truncated cylinder, the effect of elongation is perhaps appreciably accentuated. That the shape is not quite elliptical is seen from Figure 1, where the measured widths are somewhat lower than that expected, although the lengths are about correct.

The naked surface of *Arbacia* eggs is apparently liquid, as indicated by experiments on coalescence (Chambers and Kopac, 1937). The outer layers are more solid in nature (Chambers, 1940; Kopac, 1940). However, it is likely that a certain amount of plastic flow may take place in the surface. This results in a hysteresis phenomena as is observed in protein membranes (Harvey, 1936). This property would tend to reduce γ_0 to some extent. But it is likely that the measured value used above includes such an effect. Another factor not taken into account is the possible effect of volume elasticity (Pfeiffer, 1937). However, E. Howard (1931) finds no evidence of plastic flow in *Arbacia* protoplasm over a considerable range of temperature. These observations did not include the firmer layers in the region of the surface. In general, if any part of the protoplasm has an effective finite yield point, the stable shape after a deformation beyond this point would deviate from spherical depending on the value of the elastic coefficient and the yield point. There is insufficient data at present to make an estimate of such a possible effect.

As was mentioned previously, the time constants for the diffusion processes are probably well below the relaxation period. However, the initial disturbance in the diffusion fields, due to the deformation of the cell as well as to the presence of the deforming mechanism, might result in a force which tends to keep the cell slightly deformed. Thus the cell might approach a shape which is not a sphere (House-

holder, 1941). The latter shape would reduce to a sphere at a rate depending upon the time constants, Λ , of the metabolites.

In view of the above factors, one cannot rely on the estimated value of η_e as given above, but its order of magnitude may well be correct. At least it is not necessary to assume such a large value as is indicated by the analysis on the basis of a surface tension (Harvey and Shapiro, 1941).

The data on *Chaetopterus* eggs given by E. N. Harvey and H. Shapiro do not cover a sufficient range to determine a permissible range for γ_o . However, if we neglect its effect and use equation (10), together with the relation $\epsilon = R^{2/3} - 1$, the data in the range given lie close to the theoretical curve for which η/ζ is about fifty. The surface forces for *Chaetopterus* eggs are quite comparable as to order of magnitude with *Arbacia* (Harvey, 1931). If ζ should have the same value in each case, the viscosity in this case would be about one hundred and fifty times that for *Arbacia* eggs.

Summary. An expression for the length and width of a cell, which has been given an initial deformation, as a function of time is derived by an approximate method on the assumption that the surface of the cell may be elastic. The expression is found to agree with data from *Arbacia* eggs but the value of the initial surface force is not more than about one-third of that obtained by fairly direct measurements. Some of the factors that may be responsible for the discrepancy in the initial surface force are discussed. The value of the viscosity thus estimated is of the order of that of the fluid part of the egg as determined experimentally.

The author is indebted to Dr. N. Rashevsky and Dr. A. S. Householder for reading and discussing the manuscript.

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LETTER TO THE EDITOR

AN EXPLANATION OF SPASTIC WALK DUE TO ENCEPHALITIS LETHARGICA

In 1925 the writer suffered from an attack of ENCEPHALITIS LETHARGICA; was paralyzed on the left side; apparently made a complete and rapid recovery. In 1935, after ten years of freedom from after-effects, sclerosis apparently began—a slight spasticity in walking was noted developing on the left side. The flexor muscles' reflex time gradually became less than the tensor muscles' reflex time, causing a "kick-up" in walking. This has grown to be quite noticeable and does not disappear with the Belladonna treatment for after-effects.

The kick-up can be explained with a simple assumption:

$$\frac{(\Delta t_E)_W}{(\Delta t_F)_W} = \frac{(\Delta t_E)_R}{(\Delta t_F)_R} = C, \text{ a constant} = 1, \text{ for normality.}$$

Here

$(\Delta t_E)_W$ = reflex time for extensor muscles at a walk.

$(\Delta t_E)_R$ = " " " " " at a run.

$(\Delta t_F)_W$ = reflex time for flexor muscles at a walk.

$(\Delta t_F)_R$ = " " " " " at a run.

Clearly

$$(\Delta t_E)_W >> (\Delta t_E)_R$$

and

$$(\Delta t_F)_W >> (\Delta t_F)_R.$$

Then from the first assumption:

$$(\Delta t_E)_W = C(\Delta t_F)_W$$

and

$$(\Delta t_E)_R = C(\Delta t_F)_R.$$

Let us define Δ_W as the difference in reflex times for the extensor and flexor muscles at a walk; Δ_R as the difference in reflex times for the extensor and flexor muscles at a run.

Then

$$\Delta_w = (\Delta t_E)_w - (\Delta t_F)_w = (C - 1) \times (\Delta t_F)_w$$

and

$$\Delta_R = (\Delta t_E)_R - (\Delta t_F)_R = (C - 1) \times (\Delta t_F)_R.$$

But Δ_w is a measure of the kick-up at a walk, and Δ_R is a measure of kick-up at a run. By inspection it is obvious that $\Delta_w > > \Delta_R$. This is precisely what I observe, for although I have a pronounced spastic walk, *when I run the kick-up vanishes*. This result, shown by my simple analysis, is a source of surprise to all who observe my running, yet it affirms the correctness of my simple first assumption.

Pasadena, Calif.

March 28th, 1942

FREDERICK R. HIRSH, JR.

SCOPE OF THE BULLETIN

1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.
2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.
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In writing equations, slanted lines should be used wherever possible.

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